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Medical Research Mission to the Soviet Union

A. Baird Hastings and Michael B. Shimkin

Functions and Development of a Tropical Marine Laboratory

F. G. Walton Smith

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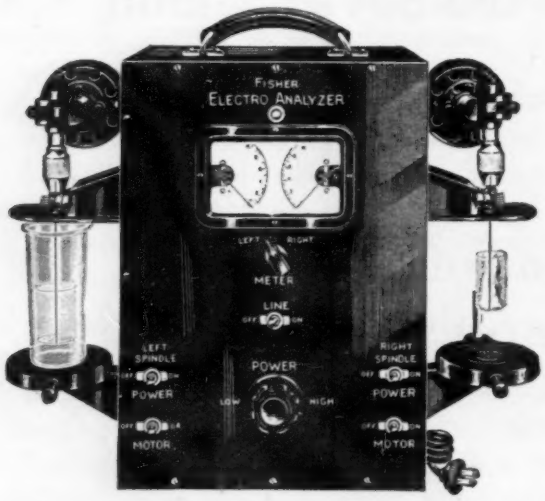

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SCIENCE

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Medical Research Mission to the Soviet Union

A. Baird Hastings and Michael B. Shimkin

IN 1943 THE SOVIET GOVERNMENT suggested to the United States Government that there be an exchange of information on certain aspects of medical research of mutual interest to both countries. Appropriate steps to effect this were taken through the United States Embassy in Moscow, the Department of State, and the Office of Scientific Research and Development.

A series of 10 subjects in which there had been active, recent research developments in the United States were selected by the Committee on Medical Research of the OSRD, and reports on these subjects were prepared by American scientists for transmittal to the medical authorities of the Soviet Union. The subjects of the reports were: "British Anti-Lewisite," by Milton C. Winternitz; "Penicillin," by Robert D. Coghill and Chester S. Keefer; "Typhus Vaccine," by Norman H. Topping, Richard G. Henderson, and Charles C. Shepard; "Plasma Protein Fractionation," by A. Baird Hastings and Edwin J. Cohn; "Quinacrine," by James A. Shannon; "Surgical Problems—Wound, Burns, Shock," by Allen O. Whipple; "Insecticides," by W. E. Dove; "Air Sterilization," by O. H. Robertson; "Dermatophytosis," by J. Gardner Hopkins; and "Goggles for Military Use," by Walter R. Miles.

Because most of these problems had been developed jointly by investigators of Great Britain, Canada, and the United States and because there had been exchange of information among the workers, the Medical Research Council of Great Britain and the National Research Council of Canada were invited to participate in the exchange of information with the Soviet Union. The reports were sent to both organizations for their comments, criticism, and additions, and these were incorporated in the reports.

It was further agreed by the Governments of the Soviet Union and the United States that the reports should be delivered in person by representatives authorized to discuss them with designated Russian medical authorities. Vannevar Bush, director of the OSRD, appointed the authors to carry out this mission.

The medical authorities of Canada and of Great Britain were informed of these appointments and were asked whether they too desired to send personal representatives. H. W. Florey and A. G. Sanders, of Oxford University, were appointed to present the medical research developments of Great Britain with particular emphasis on the methods of laboratory production and clinical use of penicillin. The medical authorities of Canada delegated their representation to Drs. Florey and Sanders.

The report of the American representatives, submitted to the OSRD, has now been released. The major observations and conclusions, with additions to bring certain information up to date, are presented here.

Itinerary

We arrived in Moscow on 14 January 1944 and left on 11 February.

After proper introductions had been made by the United States Embassy with the Soviet Foreign Office, a program of visits to laboratories and conferences was arranged by V. V. Parin. At the time of our visit, Prof. Parin occupied a position corresponding to that of A. N. Richards, chairman of the Committee on Medical Research. He taught physiology at the Third Moscow Medical Institute in the morning and attended to his activities in the Commissariat of Public Health in the afternoon and evening. Prof. Parin accompanied us on visits to three Institutes, but aside from this, we were not escorted by any government officials or interpreters. Our discussions with Soviet scientists were carried out freely and informally as scientist with scientist.

All-day visits were made and conferences held, in chronological order, at the following institutions:

Department of Physiological Chemistry, VIEM —21 January

Dr. Hastings is professor of biological chemistry, Harvard University Medical School, and a member of the Committee on Medical Research, OSRD. Dr. Shimkin is a surgeon in the U. S. Public Health Service and assistant chief of the Office of International Health Relations.

Institute of Hematology and Blood Transfusion	—24	January
Central State Medical Library	—25	"
Central Institute of Microbiology and Epidemiology	—26	"
First Moscow Medical Institute, preclinical and hospital	—28	"
Department of Education, Narkomzdrav	—28	"
Institute of Biology Section of Academy of Sciences	—29	"
Botkin Hospital	—31	"
Central Institute of Disinfection	— 1	February
Department of Biochemistry of Microbes and Immunity	— 2	"
VOKS	— 4	"
Medsantrud Hospital	— 5	"
Medical Research Council, USSR	— 5	"
Physiology Institute of Academy of Sciences	— 7	"
Neurosurgery Hospital in the name of Semashko, VIEM	— 8	"
Sklifasovski Hospital	— 9	"
Academy of Sciences, USSR	—10	"
Reception by Commissar G. A. Miterev	—10	"

We would like to make grateful acknowledgment to Commissar G. A. Miterev, Prof. V. V. Parin, Ambassador W. Averell Harriman, and members of the United States Embassy in Moscow for their many kindnesses to the mission.

Organization of Medical Research in the Soviet Union

In 1941 there were 223 separate Institutes in which medical research was carried on in the Soviet Union. These institutions had 19,000 scientific workers of different degrees of training and competence on their staffs. Administration of these research centers is primarily under the Commissariat of Public Health and the Academy of Medical Sciences. A graphic presentation of the organization of medical research is given in Fig. 1.

Commissariat of Public Health.[1] Medicine and medical research is highly organized and administratively centralized in the Soviet Union. The chief government agency is the People's Commissariat of Public Health (Narkomzdrav, a combined abbreviation of *Nar*odny *Kom*issariat *Zdravo*-okhraneniya—literally, People's Commissariat of Health Protection). It was established in 1918, but since then has acquired additional responsibilities. In 1930, for example, all medical education was placed under it in order to expedite the desired increase in the medical personnel of the country. At present the Commissariat is the chief authority in all matters pertaining to the training of physicians, dentists, nurses, and subprofessional medical assistants, to the allocation of personnel and hospitals, polyclinics, and other medical establishments, and to the medical relief, sanitation, and prophylactic measures among the population. It supervises directly the production of drugs and biological, medical instruments, spectacles, etc. and has its own publishing house ("Medgiz") for medical books and journals. At the time of our visit it also supervised most of the medical research carried out in the Soviet Union. This has since been changed, as will be discussed later. One of the few activities usually associated with medicine over which it does not have jurisdiction is veterinary medicine.

In the Soviet Union the commissariats of the USSR are reduplicated in each Republic, in which matters of regional interest are handled. Thus, there is a Narkomzdrav SSR for the Ukraine, Belorussia, and the rest of the Soviet Republics. The heads of these SSR commissariats are selected by the Supreme Soviet of the Republic, with the approval of the Narkomzdrav of the USSR.

The present People's Commissar (now Minister) of Public Health of the USSR, a position roughly equivalent to a Secretary of our Cabinet but exceeding it in authority, is G. A. Miterev.

In 1943 the work of the Narkomzdrav USSR was divided among six vice-commissariats, each headed by a vice-commissar, as follows: therapeutic facilities and organization—S. A. Kolesnikov; medical research and education—V. V. Parin; personnel and hospital allocation—S. I. Milovidov; sanitation—A. Y. Kuznetzov; special medical industries—A. G. Natradze; and maternal and child affairs—M. D. Kovrigina.

Since our visit the vice-commissariat of research and education has been abolished, the research functions being transferred to the newly-formed Academy of Medical Sciences. V. V. Parin is now the secretary of this Academy. The department of education has been shifted under another vice-commissariat. N. N. Priorov has replaced Kolesnikov, who retains his post as head of the Soviet Red Cross and Crescent Society. A veterans' hospital department has been established under the vice-commissariat of hospital allocation.

The medical research institutes under the Narkomzdrav are directed with the advice of the 16 or 17 committees of the Medical Research Council (Uchonoi Meditsinki Soviet), which examine their research plans, personnel and equipment needs, and the budget. The members of the Council are selected by the Commissariat from among the outstanding scientists of the nation. The present president of the Council is N. N. Burdenko; I. P. Razenkov is the vice-president;

[1] In March 1946 the Supreme Soviet abolished the title of Commissar and substituted the title of Minister. The present proper designation for the Commissariat of Public Health, therefore, is the Ministry of Public Health. "Narkomzdrav" is now presumably "Minzdrav."

and L. A. Koreisha is the secretary. The decisions of the Council are transmitted to Narkomzdrav, where final decisions are made in meetings of the People's Commissar with his vice-commissars and departmental heads.

Most of the institutes under Narkomzdrav are engaged in work on special problems of practical interest. Thus, there are special institutes of traumatology, prosthesis, orthopedics, industrial hygiene, sanitation education, etc. If the institutes have branches, the chief institute is designated as the Central Institute. The Narkomzdravs of the Republics have their own special institutes, which are directly under their jurisdiction and are not connected with the USSR institutions. We visited three of the Central Institutes and Special Institutes but none of the branch Institutes.

Included in the administration of the Narkomzdrav of the USSR is a group of 12 Central Institutes (CM), which by law must have a branch in each Republic of the USSR. The branches are budgeted through the local Narkomzdrav SSR, and the work is coordinated with local needs, but its chief research plans and directions emanate from the particular Central Institute of which it is a branch. The 12 Central Institutes are: (1) Tuberculosis, (2) Skin and Venereal Diseases, (3) Microbiology and Epidemiology, (4) Oncology, (5) Neurosurgery, (6) Endocrinology, (7) Otolaryngology, (8) Ophthalmology, (9) Plague, (10) Malaria and Tropical Diseases, (11) Obstetrics and Gynecology, and (12) Pediatrics. As is evident from the names, many of these are engaged chiefly in research directly related to clinical problems.

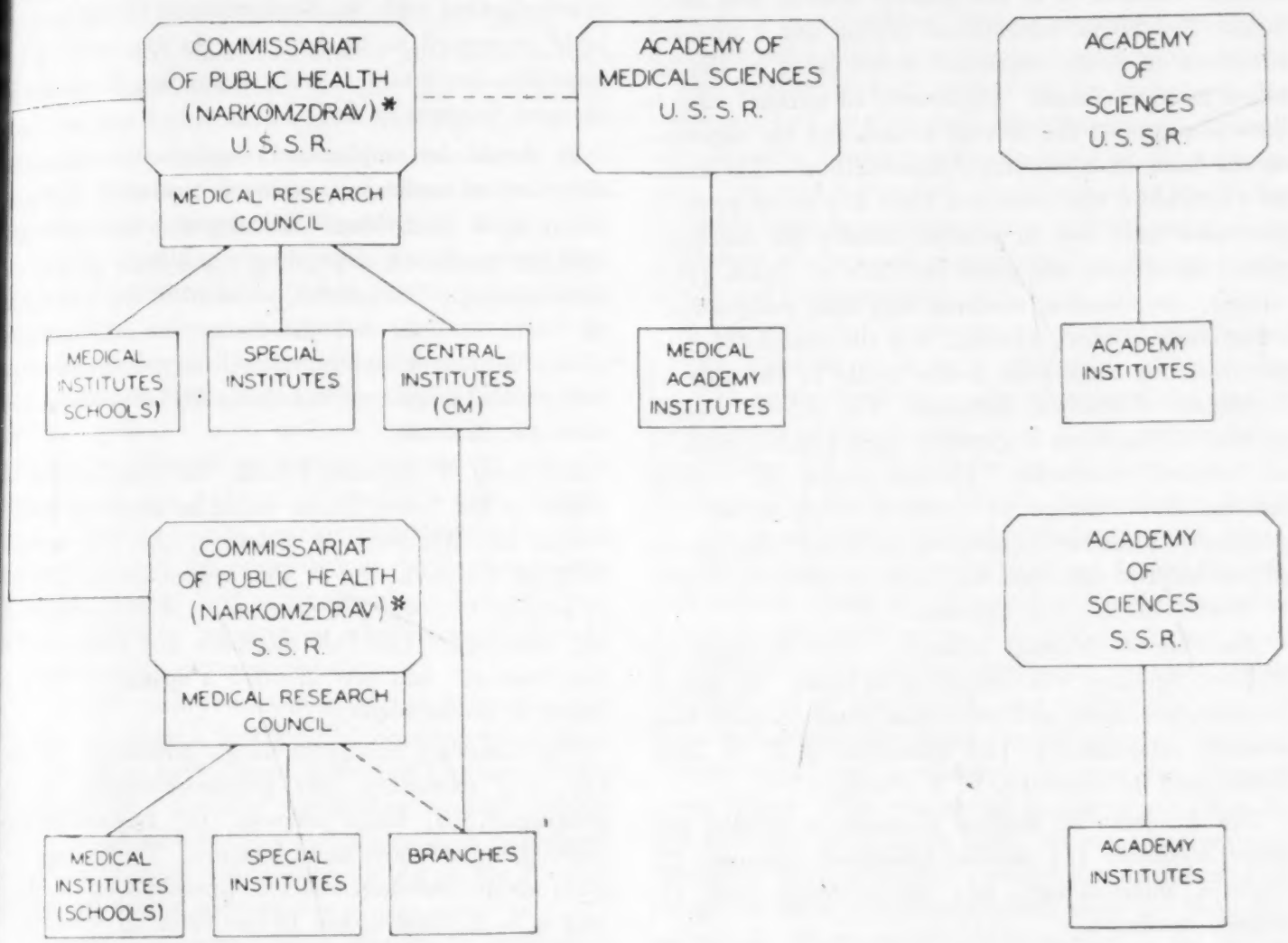

FIG. 1

* As of March 1946, Ministry of Public Health (Minzdrav).

There are 51 medical institutes (schools), 21 stomatologic and pharmacologic institutes, and 11 postgraduate institutes in the Soviet Union. The 72 medical, stomatologic, and pharmacologic institutes are designated as Medvuz (combined abbreviation of *Med*itsinskii *v*ishiye *u*chebniye *z*avedenya, or medical-highest-educational-institutions). Each department of the medical schools is required to conduct scientific work as well as the teaching of students. The research programs of the departments are examined by a council of professors and approved by the dean of the school. In the case of four or five medical schools located in Moscow and Leningrad which are directly under the jurisdiction of Narkomzdrav USSR, the research programs are further reviewed by the Medical

Research Council and approved by the Commissariat. The remainder of the medical schools are under the jurisdiction of the Narkomzdravs of the Republics, and their research programs are examined and supported by the respective local commissariats.

The training of most of the individuals engaged in medical research is in the medical schools and institutes. The Soviet educational system has a primary education of seven years and three years in the so-called middle schools. Applicants to medical schools have to complete the 10-year course and are admitted on the basis of competitive examinations. The medical curriculum was increased from five to six years in December 1944 and in general follows the American plan. Graduates are given the title of Vrach (physician). Outstanding students may take postgraduate research or clinical training, and the successful completion of a three-year course leads to the title of Candidate of Medical Sciences. The title of Doctor of Medical Sciences is granted upon further work of an original character. Professorships of medical schools, directorships of research laboratories, and positions of similar importance are filled from among physicians and scientists who have attained the degree of Doctor of Medical Sciences.

Academy of Medical Sciences. The Academy of Medical Sciences was organized in 1944. It has 60 founding members, and additional members have been selected subsequently. Its president is N. N. Burdenko, and its secretary, V. V. Parin.

The Academy of Medical Sciences is divided into three sections: (1) medical-biological sciences, (2) hygiene, microbiology, and epidemiology, and (3) clinical medicine.

The Academy absorbed the All-Union Institute of Experimental Medicine (VIEM), which had some 13 departments in Moscow and 6 in Leningrad.

The medical-biological section of the Academy is made up entirely of institutes formed from the VIEM, and the section on clinical medicine includes the neurology clinic of the VIEM. The primate station in Soukhoumi serves the needs of the Academy as a whole. The personnel previously under VIEM numbers about 2,000, of which 500 are scientific workers and, of those, 85 are of professorial rank. N. I. Grashchenkov, the previous director of VIEM, is now one of the vice-presidents of the Academy of Medical Sciences.

In addition to the VIEM, certain special institutes, such as the Central Institute of Hematology and Blood Transfusion, have been incorporated under the Academy. The total number of institutes under the new Academy is now approximately 25. Selection of the institutes was apparently made on the basis of scientific achievement and importance of such institutions, and the main objective appears to be to strengthen fundamental medical research rather than the practical research and development characteristic of the institutes directly under Narkomzdrav.

Administratively, the Academy of Medical Sciences is coordinated with the Narkomzdrav USSR, particularly in regard to its budget. So far, none of the Republics has established corresponding Academies of Medical Sciences at their levels.

It should be emphasized that the administrative structure of medical research, as presented in Fig. 1, is not rigid. Individual institutes may be transferred, split, or combined, depending upon their growth and development. The official position of the director of an institute does not determine its administrative place. Moreover, one individual may, and often does, hold several posts simultaneously and may direct more than one institute.

Academy of Sciences, USSR. No discussion of research in the Soviet Union would be complete without noting the Academy of Sciences, the top scientific body of the country. It was organized in 1724 and at present has over 200 members and 300 corresponding members. The full members are designated as Academicians and are afforded a special position of honor in Soviet society.

The Academy has seven large divisions: (1) biology, (2) chemistry, (3) physics-mathematics, (4) geography, (5) social sciences, (6) technology-engineering, and (7) arts and literature. The biology division, whose chairman and vice-president of the Academy is L. A. Orbelli, has 12 institutes, of which 9 are in Moscow and 3 in Leningrad.

There is no direct connection between the Academy and the Narkomzdrav, although the Academy is naturally well represented on the Medical Research Council. The budget of the Academy is separate from that of the Narkomzdrav.

Five of the Republics—Ukraine, Belorussia, Uzbekistan, Armenia, and Georgia—have their own Academies of Sciences. These are entirely separate from the USSR Academy and are of regional importance and significance. Some of these Academies of Sciences SSR have their own institutes.[2]

An account of visits to individual laboratories and hospitals is to be published in next week's issue of *Science*.

[2] For more detailed accounts of the Academy of Medical Sciences and its incorporation of the VIEM, see N. I. Propper-Grashchenkov (*Amer. Rev. Soviet Med.*, 1944, **2**, 108) and J. Heiman (*Amer. Rev. Soviet Med.*, 1945, **3**, 64); of organization of medical education, M. B. Shimkin (*Amer. Rev. Soviet Med.*, 1944, **1**, 465); of the Academy of Sciences, USSR, F. E. Brasch (*Science*, 1944, **99**, 437).

Functions and Development of a Tropical Marine Laboratory

F. G. Walton Smith
University of Miami Marine Laboratory

A LITTLE OVER TWO YEARS AGO, the late Dr. Thomas Barbour was kind enough to draw attention to the newly organized Miami Marine Laboratory (*1*). With the end of the war and the focusing of attention once more upon peacetime objects of investigation, the present time is well suited to a discussion of the activities which would justify any considerable expenditure of energy and money in the future development of a tropical marine station. The increase in number of marine laboratories during the past half century renders it particularly important that a new station should fulfill a real need and that it should neither overlap in function the older, established institutions nor merely add unnecessarily to the number of smaller seaside laboratories. For this reason, considerable thought has been given at Miami to the possibility of developing aspects of marine biology and oceanography which are particularly suited to the area or which are not already being adequately covered elsewhere.

The growth and development of the sciences which converge in marine biology and oceanography arose from the early expeditions following Captain Cook's voyage in 1768. Further expeditions in which oceanographic sampling and other techniques were introduced took place in later years, culminating in the specialized cruises of the present day.

The work that ocean cruises are able to accomplish is limited, although it is indispensable for a knowledge of the fauna and flora of the open sea, of the nature and organisms of the sea bottom, and of the ocean currents and physical characteristics far from shore. It is not suited, however, for anatomical, histological, physiological, and embryological inquiries, for long-term investigations into seasonal variations of seawater and its plankton, or for close and careful coastal ecological studies. The need for these investigations brought into existence numerous seacoast laboratories after the opening of the celebrated Naples station, in 1872. These are to be found, with few exceptions, on seacoasts in temperate latitudes, and, as a result, the classical work in marine biology and oceanography refers principally to the open ocean or to these temperate shores. The centers of population and civilization are at neither the Poles nor the Equator but are in the temperate latitudes, while the great fishing industries are based on the chemically rich, shallow banks of the temperate Atlantic and Pacific. There have been no equivalent stimuli to marine biological and oceanographical investigations on tropical shores.

The volume of work turned out by stations in the temperate latitudes has been remarkable, and it is now true that the broad general features of the physics, chemistry, and biology of coastal waters in the higher latitudes have been blocked out. The general characteristics of the open oceans are also known in certain broad fundamentals.

In contrast, our ignorance of tropical shores and waters adjacent to them is profound. This is not hard to understand when we enumerate the marine laboratories of the tropics. One of the earlier tropical stations was that founded by the Carnegie Institution at Dry Tortugas, Florida, faunistically within the tropics, although geographically just outside. Inaccessibility was one of the factors that forced this station to close, much as it brought about the closure of Agassiz's laboratory on the island of Penikese. Some 40 years ago a station was opened on Bermuda which, although not in the tropics, was sufficiently close to them and sufficiently under the influence of the Gulf Stream to support a relatively impoverished tropical ocean fauna. This was closed during World War II, and now that it is again open, its comparative inaccessibility may somewhat restrict its usefulness, although its value as an oceanic base must not be underestimated. There are also small stations in the Philippines, in Hawaii, and at the University of Texas.

In addition to this hiatus in our knowledge of marine biology and oceanography, there is a further argument that may be advanced in favor of a tropical marine laboratory. It would fulfill a definite demand in providing unusual advantages for the study of the constituent sciences themselves, considered independently of oceanography. The terrific competition for food and space on the living coral reefs and the enormous variety of species, of adaptations, of feeding habits, and of methods of attack and defense, make it a classroom and a workshop for the study of fundamental branches of biology. Furthermore, the physiologist, behaviorist, ecologist, embryologist, or biochemist who uses marine animals and plants merely because of their convenience and not because of an interest in the ocean is immensely benefited by being able to work at a tropical station where the organisms are active the year round.

These conditions exist in the Miami area. Not only

is it tropical in the sense that its shores harbor the representative West Indian flora and fauna, but it also has accessibility, lack of which contributed to closing of the Dry Tortugas laboratory. Ocean beaches, mangrove swamps, and wide areas of coral reefs, shallow water, and flats form only part of the extraordinary variety of environmental conditions. The coral reefs are in shallow water so that collecting with a diver's helmet is perfectly practicable, and the Gulf Stream is closer than at any other part of the Atlantic Coast.

The islands of the West Indies and of the Caribbean Sea have many interesting problems. Various factors have made it difficult to establish a satisfactory marine laboratory on these islands, although this has been proposed many times and has again been broached in recent years (*2, 3*). The problems of the West Indies, however, are the problems of south Florida, and the accessibility of Miami by airplane, railroad, and boat, from the West Indies and the scientific centers of the United States alike, increases the opportunity for studying these problems here.

The above reasons, coupled with the necessity of carrying out certain phases of marine research important to the prosecution of the war in tropical waters, brought about the Miami Marine Laboratory as a logical process, greatly assisted by the cooperative interest of the Woods Hole Oceanographic Institution.

In order that the geographical advantages of the location may be utilized to their fullest extent, the aims and functions of the Laboratory are being formulated with care. In the first place, it is realized that in order to attain its widest usefulness a tropical laboratory must be more than a mere adjunct of one university. It must provide a definite service for biologists at large, and the requirements and opinions of these biologists must be considered in the further development of the institution.

It is further realized that in order to develop our knowledge of tropical oceanography and biology it is not sufficient to provide facilities for visiting investigators. There must be a permanent staff, however small, to work within a definite program of investigation, correlated with investigations already completed and others still continuing in temperate latitudes.

It is believed that a proper balance should be struck between academic and applied investigation, and that to some extent each gains by its proximity to, and relations with, the other. On the academic side the investigations which have been considered include biological studies of the more important marine flora and fauna, from the viewpoints of taxonomy, embryology, physiology, and ecology; the studies of seasonal plankton variations and their relations to chemical and physical conditions of the bay and open ocean; and the general question of total organic productivity. Hydrographical studies, including the dynamics of the Gulf Stream, should be carried out in collaboration with institutions engaged in this work elsewhere.

Applied marine science in the tropics has been somewhat neglected. Certain fields, such as sea-water corrosion, ship-fouling prevention, and preservation of submerged structures, may be investigated in the tropics with especial advantage, because of the enhanced rate at which the destructive agencies operate as compared with temperate waters, and because of the year-round opoprtunity for field work, unimpeded by climatic changes.

Not only south Florida but the whole of the West Indies are backward in the investigation of marine industries, except where they are of such a nature that Federal agencies may be called in. The natural production of these latitudes is lower than that of temperate regions, the importance of fisheries varying accordingly. Nevertheless, a limited program of fisheries work is justifiable, and it is hoped that future developments may fall somewhat in line with the recommendations of the Anglo-American Caribbean Commission (*4*).

The fishes that might provide reasonably large-scale commercial fishing in the West Indies are, with certain exceptions, the pelagic migrants, so that the most obvious phase of the work is the investigation of movement, life histories, and spawning habits of migratory fish, as well as the study of local fish.

Investigations of edible marine products not hitherto utilized will tend to ensure more economical operations for fishermen. The investigation of methods of handling may bring about the same end and should not neglect the methods of handling used at sea. The fisheries technologist should be concerned with the effectiveness of types of fishing gear employed, the collection of fishery statistics, and the evolution of sound conservation methods. The biochemist has his problems of utilization of by-products and the toxicology of tropical fish poisoning.

Training in the various fields of tropical marine science is equally important. Articles in the national journals of at least two countries have expressed the desirability of instruction in tropical biology as a part of the training of every professional biologist (*1, 3*). This is particularly true in view of the economic development of tropical countries in recent years. In keeping with the general policy, it is felt not only that courses should continue to be given by the staff of the Marine Laboratory, but that as facilities are increased, the faculties of inland and northern universities and schools should be encouraged to bring field classes here during vacation and, should they wish, give instruction themselves at times when the regular courses are not offered.

The educational plans of the tropical marine laboratory should also include consideration of the advisa-

lity of technical training, not only in the form of dvanced academic and technological training for arine scientists and fisheries officers, but also a prac- al vocational short-term intensive training of fish- rmen selected for their leadership in the various com- unities of Florida and the West Indies, where gov- rnment scholarships would be needed.

This program is, of course, ambitious and compre- ensive. It will have served its purpose if put into ractice in a few directions which appear most prac- al and receive the most encouragement. The pro- ram is, in fact, already being realized to some extent.

Seasonal changes in the chemical and physical con- nt of the sea water, including phosphate, nitrite, linity, and dissolved oxygen, are being studied by onthly observations at 11 stations chosen for their ide ecological differences. At these stations simple antitative and qualitative plankton determinations re made. Parallel observations are being made on rganisms attaching to the underside of floating rafts, such a manner as to provide evidence not only of easonal changes but also of succession.

The teaching program has not been neglected, and he elementary courses in marine botany and zoology tarted over 15 years ago are still being continued. n addition, graduate courses are now offered in the niversity in the fields of oceanography and marine iology. These include courses in oceanographical hysics and chemistry, marine algology, the biology f fishes, ecology, including statistical fisheries tech- iques, and invertebrate taxonomy and embryology.

In applied fields of science the facilities and per- onnel of the Laboratory have been utilized by various aval and military groups and by the Woods Hole ceanographic Institution for work of importance to he war effort. Surveys of the behavior and distribu- ion of fouling organisms are now being continued ndependently by the staff. Preliminary work is also eing carried out on deterioration of cordage in sea ater and the influence of marine bacteria in deteri- ration of lubricated metal surfaces. A study has een made of the rate of growth, productivity, and the hemical utilization of tropical marine algae.

In spite of handicaps, a start at least has been ade in the field of fisheries research, and an investi- ation is at present being conducted into the Florida piny lobster industry, in collaboration with the State Conservation Department. A similar survey as also been organized for the Bahamas Government, tilizing government personnel. The use of the log- erhead sponge and other hitherto valueless marine roducts as a source of organic fertilizer has been nvestigated.

Since it has been suggested in some quarters that a tropical marine laboratory in south Florida or the West Indies should be part of a tropical biological laboratory covering both marine and terrestrial phases, mention may also be made of activities not strictly within the field of marine biology.

A relatively new field is the study of causes and methods of preventing deterioration of various materials and equipment under semitropical conditions such as exist in the mangrove swamps and the damper parts of the Everglades. The peacetime significance of this type of work, in which the Miami Marine Laboratory has recently been associated with an industrial laboratory under military contract, is becoming increasingly obvious. Fabrics, all types of electrical and other equipment and machinery, and the materials and finishes employed in building and vessel construction are subject to deterioration from the effects of salt air, moisture, and fungus growth in the tropics, and with increasing competition for trade in tropical countries, this factor will assume even greater importance. In south Florida field tests as well as laboratory investigations are possible in the mangrove and Everglades swamps.

The present quarters are of a temporary nature and do not offer altogether suitable accommodations for the staff, equipment, and motor vessel. Funds for operation are received partly from irregular contributions from other institutions, governmental agencies, and industrial concerns in return for participation in specific projects and partly from the general funds of the University of Miami. In order to facilitate further development it will be necessary to secure a permanent building and a more regular and extensive source of funds, not merely for specific projects but for general upkeep and maintenance, for the sustaining of fundamental research, and for provision of hospitality to visiting investigators.

The problem of a permanent building may shortly be solved. The Dade County Commission has agreed to collaborate with the University of Miami by building a $2,000,000 Oceanarium and Marine Laboratory. The Oceanarium is being planned by, and will be operated under, the direction of the Marine Laboratory staff, and adequate modern laboratory facilities will be provided.

Future development will depend upon the extent to which the facilities are utilized. In order that growth of the Laboratory may take place along the lines of greatest benefit to the sciences concerned and in order to encourage future participation and support, the recommendations and suggestions of interested scientists will be welcomed.

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Obituary

Edwin Bissell Holt

1873-1946

Psychology and the world of knowledge in general lost an original and a universal mind in the death of Edwin Bissell Holt on 25 January 1946. Though the formal recognition accorded to him during his life was scarcely proportionate to his greatness, his name will occupy a prominent place when the historian records the uneven progress of psychology in the first part of the Twentieth Century.

E. B. Holt was one of that brilliant group of students of William James who became influential not as exponents of a James system of psychology but as founders of the science of psychology in this country. From 1901 to 1919 Holt was a member of the psychology faculty at Harvard University; from 1926 to 1936 he was visiting professor at Princeton.

His *Concept of consciousness* (1914) anticipated his motor theory of psychology and was more important philosophically than psychologically. His *Freudian wish* (1915), however, has become a classic in American psychology. Academic psychologists, working in their laboratories, had developed an account of man as an assembly of sense organs and reflexes. Freud, working as a physician dealing with mental disorder, had produced world-shaking theories about the motivation of human behavior. Traditional academic psychology saw no way of relating its world of discourse to the Freudian realm. It was the genius of Holt that translated and modified Freudian doctrines into the terms of behavioral science. The progress of psychology in the past 30 years has been, to a considerable extent, the implementing and elaborating of Holt's contribution in *Freudian wish*. This work is also a milestone because it rejected the artifactual elementarism of the time and emphasized the importance of regarding behavior not as the summation of reflexes but as a function of the field of forces.

Holt is perhaps best known for his motor theory. The early behaviorists repudiated the conventional areas of psychology relating to conscious experience and concentrated upon a study of behavior. The effect of Holt's teachings was to strengthen this movement, but his own motor theory was much in advance of Watsonian doctrine. It attempted to deal with all conscious experiences by identifying them with their motor patterns of response. Many experimental studies in thinking and perception stemmed from the Holtian theory. Unfortunately, little of Holt's work on the problem was in print until *Animal drive and the learning process* appeared in 1931. This work was as late in relation to public interest as his *Freudian wish* had been early. If *Animal drive* had appeared 10 years earlier, it would have given the behavioristic movement a rationale, a perspective, a balance, and a sophistication which it desperately needed. Nevertheless, this work remains the most complete and the most scientific account of human psychology from a mechanistic or materialistic approach. It combines the philosophical recognition of the important problems of the older European writers with the scientific discoveries in modern neurology and psychology. Unfortunately, Holt ignored the entire area of constitutional and glandular factors in the determination of human nature and made no serious attempt to evaluate the evidence in this field. His account of man suffers, in consequence, from a neglect of the internal chemical environment of the organism.

The breadth of Holt's mind is indicated by mentioning two more specific contributions, one to epistemology and the other to social psychology: (1) The Berkeley doctrine of idealism, which asserts that reality inheres not in a world external to ourselves but in our sensations and ideas, never received as systematic and psychologically devastating an answer as Holt's article in the *Psychological Review* of 1914 which exposed the fallacious psychological assumptions on which Berkeley rested his argument. (2) In the social field Holt suggested the fundamental approaches and swept aside the pious hokum and verbalism that sometimes passes as social science. At Harvard, his lectures in Social Psychology comprised one of the first courses to be offered in this field. A cryptic summary of his contribution can be found in his article, "The whimsical condition of social psychology and of mankind," which appeared in *American Philosophy Today and Tomorrow* (1935).

The discrepancy between Holt's real influence on American psychology and its recognition was due to his indifference to the accepted institutional channels of the profession. He did not attend meetings or present papers at conventions; he set no store by quantitative publication in the journals.

Holt was probably the last great American psychologist in the European tradition of philosopher-scientist. His own experimental studies were few, but his systematic formulation of theory and his wise and brilliant evaluation of research findings suggest that there is still a place for the philosopher-scientist—even in modern psychology.

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Technical Papers

The Purification and Crystallization of *Clostridium botulinum* Type A Toxin [1]

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A preliminary report is presented of a method which has permitted the isolation at will of highly toxic needle-shaped crystalline protein material from a Type A culture of *Clostridium botulinum*. Electrophoretic analysis shows a single component.[3] The capacity of this material to react in a flocculation test with commercial antitoxin and to have its pharmacological activity neutralized by such antitoxin suggests the isolation of the Type A toxin concerned in food poisoning. The method builds upon the basic observations of Snipe and Sommer (*3*) and Sommer (*4*) that the toxin is acid precipitable from culture medium and can be eluted from the acid precipitate by buffer solutions at appropriate pH values.

Five-gallon carboy lots of a 0.3-per cent casein, 0.5-per cent glucose, and 1.0-per cent alkali-treated corn steep liquor medium (*1*) at pH 7.2 are inoculated and held at 34° C. until a maximum titer of toxin appears. This usually takes 72 to 80 hours. The method of purification and crystallization is as follows:

Step 1: The cultures are precipitated at pH 3.5 by addition of 2 N HCl. All acid-precipitable material, which includes toxin, nucleic acid, undigested casein, material from corn steep, and the organisms, is allowed to settle out overnight. The supernatant is siphoned off, and the precipitate collected in centrifuge tubes (250 ml.) at 1,800 r.p.m. The mud is washed once by resuspension in distilled water and recentrifugation.

Step 2: The washed acid mud is resuspended with the help of a Waring blender in distilled water to a volume of 300–400 ml. for each carboy of culture originally precipitated. This volume is referred to as original volume. Sodium chloride is added to one molar and sodium acetate to 0.075 molar concentration, and the pH adjusted to 6.5.

Step 3: The suspension is centrifuged at 1,800 r.p.m. to remove the coarse particles. To the supernatant one-sixth to one-tenth of its volume of c.p., chloroform is added and the mixture shaken vigorously for five minutes under CO_2. The pH drops to 5.8–6.1. The gel and excess chloroform are centrifuged off. If the original culture has 800,000 or more intraperitoneal 20-gram mouse MLD/ml., the aqueous supernatant will contain 15–30,000,000 MLD/ml. After the chloroform shaking, the pH of acid precipitation of the toxin in the presence of 1-per cent salt solutions changes from 3.5 to 5.0. The new pH value of acid precipitation is used in Step 5. In a future paper we hope to present data that permit some understanding of the function of shaking with chloroform in the purification procedure and the reason for the new pH value of acid precipitation.

Step 4: To the supernatant of Step 3, $(NH_4)_2SO_4$ is added to 20 per cent saturation (14 grams $(NH_4)_2SO_4$/100 ml. of solution). After refrigeration overnight the toxic precipitate which forms is centrifuged off. This step and the following one remove the bulk of nucleic acid present.

Step 5: The toxic precipitate of Step 4 is resuspended to three-fourths original volume in 0.075 M sodium acetate at pH 6.5–6.7. The pH is dropped to 5 with HCl, and the resulting precipitate allowed to settle out in the refrigerator. The pH 5 precipitate is centrifuged out and resuspended at pH 6.5 in molar sodium chloride and 0.075 M sodium acetate to one-third the original volume. In this mixture of salts the toxin is no longer precipitable at pH 5.

Step 6: The pH is then dropped to 5. Solid $(NH_4)_2SO_4$ is added in increments of 5 per cent saturation (3.5 grams/100 ml. of solution) up to 20 per cent saturation. The precipitates appearing on each addition of 5 per cent saturation are collected separately by centrifugation. The 20-per cent saturation precipitate is usually pure white and upon resuspension in 0.075 M sodium acetate gives a perfectly clear solution. The color of the 15-per cent saturation precipitate will vary from batch to batch. The 10 per cent precipitate is usually highly colored. The 5 per cent precipitate is usually not very abundant, is deep brown in color, and is discarded.

Step 7: The 20 per cent and 15 per cent precipitates are redissolved in 1/300 of the original volume (at least 240,000,000 MLD/ml.) of 0.075 M sodium acetate at pH 6.5. $(NH_4)_2SO_4$ is added, 0.1 gram/10 ml. at a time, to a total of 0.9 gram/10 ml. of solution. Any brown material remaining usually precipitates and can be centrifuged off. The resulting clear liquid has additional $(NH_4)_2SO_4$ added to give tur-

[1] Studies conducted at Camp Detrick, Frederick, Maryland, from June 1944 to August 1945.

[2] With the technical assistance of PhM1c J. F. Valentine, PhM3c N. Harmand, and HA1c S. Biscardi.

[3] We wish to thank Lt. G. Kegeles for his studies of the electrophoretic characteristics of the toxin.

bidity. After standing overnight in the refrigerator, the material coming out of solution is crystalline.

Step 8: The color of the precipitates of Step 6 has varied from batch to batch. In those cases where the precipitates remained fairly highly colored they were reworked in the following fashion. The precipitates are resuspended in molar NaCl and 0.075 M sodium acetate at pH 6.5. Insoluble material is centrifuged off and discarded. The pH is dropped to 4.0, and precipitated material is centrifuged off. This precipitate can be reworked as many times as is necessary for complete recovery of toxin. To the supernatant at pH 4.0 after centrifugation enough solid $(NH_4)_2SO_4$ is added to give 15 per cent saturation. After standing in the refrigerator the white toxic precipitate is centrifuged off and can be crystallized (Step 7). In the salt solution down to pH 3.5 the toxin apparently remains more soluble than the brown contaminating material. This fact makes the separation possible. The pH of acid precipitation of the toxin is dependent on the nature and quantities of salts present.

Crystallization from the acetate buffer has been obtained in the pH range of 5.5–7.1. It appears as though supersaturation on the alkaline side of the isoelectric point by a variety of means will result in crystallization. Adding sufficient $(NH_4)_2SO_4$ to reduce the solubility of solutions of amorphous material given the most rapid and consistent results. But $MgSO_4 \cdot 7H_2O$ and Na_2SO_4 may be used in place of $(NH_4)_2SO_4$. In some cases slow evaporation at room temperature of concentrated solutions of the toxin in acetate buffer at pH 6.5 results in crystallization.

Crystal size has been found to be dependent on the speed with which the toxin is salted out from the supersaturated solution. Apparently the fewer nuclei present, the larger the crystals obtained. Two rapid methods of obtaining large crystals are used: (a) In the case of a solution in which crystallization is going on, centrifuge off the crystals coming out first. Place the clear supernatant in the refrigerator. The crystals then coming out of solution are of a larger size than the first material. (b) Place a drop of slightly turbid crystalline suspension on a clean glass slide and cover with a cover slip. At room temperature let some of the solution evaporate from the sides of the cover slip. Then seal the preparation with paraffin and place in the refrigerator. After the large crystals have formed (few hours to overnight) by growth from smaller ones, the preparation can be kept at room temperature without disruption of the crystals. Crystals 125 μ in length and 7 μ in width have been obtained. Others average about 85 μ by 5 μ. A tendency for the crystals to line up in parallel rows with no tendency to collect in rosettes has been observed.

Recrystallization has been accomplished by supersaturation of distilled water solutions. A minimum amount of distilled water at room temperature at pH 7–8 is used to dissolve the material to be recrystallized. The pH tends to drop as the toxin goes into solution. When placed in a refrigerator, the material coming out of solution appears as the same-shaped needle-like crystals noted for the buffer solutions.

The degree of purity attained by the method is suggested by the data in Table 1.

TABLE 1

SOME BASIC DATA FOR PURIFIED *Clostridium botulinum* TYPE A TOXIN

Observation		Batch of Toxin	
		C42E	Crystalline
Nature of materials		Amorphous	C38
Electrophoresis data* pH 4.44, acetate buffer	No. of components	One	One
	Mobility, $V_D(10)^5$ Cm.²/volt/sec.	+3.2	+3.1
MLD/mg. nitrogen†		120.7×10^6	.....
LD_{50}/mg. nitrogen‡		198.5×10^6	239.9×10^6
Mg. nitrogen/MLD		8.3×10^{-9}	.....
Mg. nitrogen/LD_{50}§		5×10^{-9}	4.2×10^{-9}
Adamkiewicz test (tryptophane)		Positive	Positive
Molisch test		Negative	Negative

* Data obtained by Lt. G. Kegeles.

† MLD is defined as the smallest amount of material injected intraperitoneally which will kill six out of six 18- to 20-gram white mice within four days time.

‡ LD_{50}—calculated by R. A. Tiede by the method of Bliss (*Ann. appl. Biol.*, 1935, **22**, 134, 307).

§ Pickett, Hoeprich, and Germain (*J. Bact.*, 1945, **49**, 515–516) have reported the isolation of tetanus toxin giving $2.3–5.7 \times 10^{-8}$ mg. N_2/mouse MLD. This is the most potent toxic material known to us that has been previously reported.

The similar electrophoretic mobility for both amorphous and crystalline material is a strong argument for the isolation of a single toxic substance. The rapidity of crystallization and the agreement of data on the LD_{50}/mg. of N_2 for both types of materials are equally suggestive of a high degree of purity. The ordinary chemical tests for protein such as the Biuret and Millon's are positive. The nitrogen content is 14.3 per cent. The molecular size as indicated by the membrane diffusion method of Northrop and Anson (*2*) is rather large. Assuming a spherical shape, the radius of the molecule lies between 7.7 and 9.1×10^{-7} cm. These data suggest a molecular weight between 1,000,000 and 2,000,000. The immoderate spread in these data is attributable to a large variation in the animal titrations used for measuring the toxic diffusate. Both impure and crystalline toxin were used in making the determinations.

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The Isolation and Crystallization of Tetanal Toxin[1]

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A toxic protein from the filtrates of *Clostridium tetani* identical in behavior to tetanal toxin (spasmin) has been isolated and crystallized in this laboratory. The crystalline material contains between 3,500 and 4,000 flocculating units (Lf) and between 50,000,000 to 75,000,000 mouse minimal lethal doses (MLD)/mg. of nitrogen. This Lf value compares favorably with the figure of 3,300 Lf/mg. of nitrogen estimated on the basis of combining nitrogen to be the true Lf value for pure tetanal toxoid (*2*). The MLD content of the crystalline protein/mg. of nitrogen is at least 200 times greater than the purified toxin prepared by Eaton and Gronau (*1*), and also at least 50 per cent greater than the purest preparations of Pickett and co-workers (*4*).

The method employed for the purification and crystallization of the toxin involves the use of methanol under rigidly controlled conditions of pH, ionic strength, protein concentration, and temperature (*5*). The parent tetanal toxin used in this study was prepared by the method of Mueller and Miller (*3*). The major steps in the isolation and crystallization of the toxic protein are summarized in Table 1, together with assays and analyses of the various fractions. It will be noted that the activity of the crystalline toxin/mg. of nitrogen has been increased more than 500 times on an Lf basis and 800 times on an MLD basis over the parent toxin filtrates. Four crystalline preparations show a remarkable constancy in the Lf and MLD contents/mg. of nitrogen. The Lf and MLD units/mg. of nitrogen remained constant during three additional recrystallizations. The yield per liter of parent toxin filtrate is less than 1 mg. of nitrogen.

TABLE 1

GENERAL PROCEDURES

Preparation	No.	Mg. N/ml.	MLD/ml. $\times 10^6$	Lf/ml.	Kf* in min.	MLD/mg. N $\times 10^6$	Lf/mg. N	MLD/Lf $\times 10^4$	Yield Per cent of parent toxin
Parent toxin	..	3.01	0.2	20	15	0.066	6.6	1.0	..
Material insoluble in 40% MeOH at pH 5.2, μ 0.09, and temp. −5° C. Precipitate dissolved in 0.15 M sodium acetate.	1	0.320	5	300	10	15.6	937	1.66	95
Precipitate 1 adjusted to 15% MeOH at pH 5.5, μ 0.03, and temp. −4° C. Precipitate dissolved in 0.15 M sodium acetate.	2	0.172	4	250	10	23.2	1453	1.6	90
Precipitate 2 adjusted to 12% MeOH at pH 4.0, μ 0.075, and temp. −4° C. Precipitate discarded. Supernatant employed.	3	0.054	1.8	112	10	33.3	2074	1.6	83
Supernatant 3 adjusted to 30% MeOH at pH 4.0, μ 0.02, and temp. −6° C. Precipitate discarded. Supernatant employed.	4	0.034	1.5	90	10	44.1	2646	1.66	80
Supernatant 4 adjusted to 25% MeOH at pH 5.1, μ 0.02, and temp. −8° C. Crystals and slight amount of amorphous material formed precipitate.	5	0.041	2.25	140	10	54.9	3415	1.6	60
Precipitate 5 recrystallized as in No. 5. Crystals formed precipitate.	6	0.022	1.5	80	10	68.1	3636	1.87	45
Precipitate 6 recrystallized three times as in No. 5. Crystals formed precipitate.	7	0.015	1.0	55	10	66.6	3666	1.81	27

* Kf determined at 20 Lf units.

Crystallization of the toxic protein occurs slowly at −8° C. under the conditions shown in Table 1. The crystals disintegrate rapidly at temperatures above −5° C. and dissolve in the mother liquor at temperatures above 0° C. This behavior has presented technical difficulties in microphotographing the crystals. However, a sketch of the crystals is presented in Fig. 1.[2]

The colorless crystals dissolve instantly in 0.15 M sodium acetate at pH 6.5. The solution gives positive reactions with protein reagents. Both the Molisch test and the nitroprusside test are negative.

[1] Aided by a grant from Wyeth, Inc.

[2] We are indebted to Theodora Bergsland, medical artist at the Institute of Pathology, Western Reserve University, for her painstaking sketch of the crystals.

The crystals appear uniform and possess constant biological activity upon recrystallization. Their activity is destroyed by heat, acid, or alkali. This would indicate that the crystalline protein is identical with tetanal toxin.

Complete chemical, physical, and biological characterization of the crystalline toxin will have to await the accumulation of larger quantities of material. The detailed procedure for the isolation and crystallization of the toxin as well as its characterization will be presented at a later date.

FIG. 1. Crystals of toxic protein from filtrates of *Clostridium tetani*, magnified 430 times.

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The Effect of the Prepartum Diet of the Cow on the Vitamin A Reserves of Her Newborn Offspring[1]

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The importance of the prenatal nutrition of the calf is recognized, but the problem has been given scant consideration experimentally. Analyses of livers (*1, 3, 5, 6, 7, 8, 12*) and of blood (*14, 15*) from young calves (fetuses and newborn) revealed low vitamin A reserves. The general uniformity of these results in conjunction with observations of laboratory animals has led to the belief that the gestation diet of the dam has no appreciable effect on the vitamin A content of the fetal calf liver. Recently, however, Braun and Carle (*3*) noted that the vitamin A content of the fetal calf liver, though low, was in direct relationship to the diet of the mother. Unfortunately, conclusions from many of the data are vitiated by pathological complications in the experimental subjects.

In view of the foregoing evidence, steps were taken to ascertain the effects of the plane of carotene and vitamin A intake of the dam during the latter stages of gestation on the vitamin A reserves of the normal newborn offspring.

Procedure. The experimental subjects were healthy dairy animals of the Ayrshire, Holstein, and Jersey breeds, of which the latter constituted about 50 per cent. During the immediate prepartum period, the dams were placed under three dietary regimes with respect to the carotene and vitamin A intake: standard, high carotene, and high vitamin A. All the cows were fed a basal ration consisting of good-quality alfalfa hay, sorghum silage and a concentrate mixture. Group I (the standard, or control) was restricted to this ration, but Group II (high carotene) was grazed on pasture forage in addition, and Group III (high vitamin A) was fed a vitamin A supplement.[2] The carotene intake was undetermined, but the vitamin A consumption per cow was one million U.S.P. units daily. The prepartum period of pasture grazing ranged from 14 to 90 days, and of vitamin A supplementation from 8 to 45 days.

Samples of venous blood were drawn from the calves, usually within four hours after birth and always before colostrum ingestion. The collection of blood in the early postpartum stages was necessitated by the tendency of the vitamin A concentration in the serum to decrease in the fasted newborn (*9*). Subsequently several of the calves from dams in each group were sacrificed to obtain their livers for analysis.

The general analytical procedures adopted in the determinations of carotene and vitamin A were those of Kimble (*11*) for blood and a modification of those of Guilbert and Hart (*6*) for liver. The major deviation in the latter case was in the use of ether extract from a sample of dry tissue (dehydrated by grinding with anhydrous sodium sulfate) for saponification.

Results. The data in Tables 1 and 2 reveal no marked differences between the vitamin A reserves of calves from cows on the basal ration and those on the high carotene but a significantly higher storage in

[1] Contribution No. 162, Department of Dairy Husbandry, and No. 304, Department of Chemistry.

[2] "Dry vitamin A" supplied by Distillation Products, Inc., Rochester, N. Y.

e case of vitamin A supplementation. The results rther indicate a positive relationship between the amin A of the blood and that of the liver. In cord with observations of other investigators caroe was usually present in the serum but undetectable the liver.

TABLE 1

E EFFECT OF THE PREPARTUM DIET OF THE DAMS ON THE VITAMIN A AND CAROTENE IN THE BLOOD SERUM OF THE NEWBORN CALVES

roup	Supplements to basal ration	No. of calves	Average values for serum	
			Vitamin A	Carotene
			γ/100 ml.	γ/100 ml.
I	None	4	2.90 ± 0.42*	0.65 ± 0.38*
II	Pasture	8	2.65 ± 0.49	1.39 ± 0.47
III	"Dry vitamin A"	4	9.40 ± 0.96	1.47 ± 0.70

* Standard error as determined by *Bessel's Formula* (*16*).

TABLE 2

THE EFFECT OF THE PREPARTUM DIET OF THE DAMS ON THE VITAMIN A AND CAROTENE IN THE LIVER OF THE NEWBORN CALVES

roup	Supplements to basal ration	No. of calves	Average values for liver	
			Vitamin A	Carotene
			γ/gram*	γ/gram
I	None	3	0.49 ± 0.19	0
II	Pasture	5	0.56 ± 0.12	0
III	"Dry vitamin A"	2	6.75 ± 1.15	0

* Wet basis.

The stage in the fetal development when vitamin A upplementation was most effective in augmenting the body reserves is undetermined, but the observations made in this study revealed no advantage for periods longer than the terminal two weeks of gestation.

Discussion. A basis for further appraisal of the magnitude of the vitamin A stores in the newborn offspring may be obtained by comparing the data presented in Tables 1 and 2 with those derived from older calves. The vitamin A concentration of 9.4γ/100 ml. of serum from the prenatally supplemented newborn was about the same as noted in the colostrum-fed calves 12 hours of age (*9, 15*) and near the lower level of the range reported to be normal for young calves (*13*), presumably beyond the colostrum ingestion stage. For the livers the average value of 6.75γ of vitamin A/gram, in the group from vitamin A-supplemented dams, was considerably greater than 2.2γ/gram found in a calf 12 hours after receiving colostrum, but markedly less than 19.5γ/gram, in a calf fed colostrum for four days (*9*). It should be emphasized, however, that the values from colostrum-fed calves are subject to wide variations, due to the variable amounts of the food ingested and to the extremes in vitamin A and carotene potency of the colostrum.

The low values for vitamin A normally found in the fetal calf liver seemingly are ample for development *in utero* but inadequate for continued postnatal health. A rapid increase of the vitamin A concentration in the newborn apparently is essential in protecting it from many calfhood disorders. The first primary source of nutrients is colostrum, the vitamin A potency of which depends on the prepartum diet of the dam (*9*) as well as on other factors. Recent studies (*9*) have revealed that parturient cows under standard feeding and managerial practices occasionally do not produce colostrum, a failure that is likely to be overlooked in the average herd. Thus it appears that prenatal supplementation is an expedient means of endowing the young calf with vitamin A and of aiding in the prevention of diarrhea in the newborn (*4*).

The effect of the prenatal diet on the vitamin A reserves of the offspring introduces the conjectural issue of placental transmission and fetal storage. From the low vitamin A values normally observed in the fetal liver two principal theories have emerged: either (1) the placenta permits only limited amounts of carotene and vitamin A to pass or (2) fetal metabolism inhibits extensive storage. Evidence gleaned from the literature indicates that the placenta plays the primary regulatory role. On this premise a *placental threshold* conceivably may serve in the control mechanism. Feeding massive amounts of vitamin A thus would increase the concentration in the maternal circulation to the extent that a portion of the excess passes into the fetus. This, however, is not in accord with the low values from the pasture-supplemented group. A more feasible explanation may be found in the recognized differential permeability of the placental membrane. Possibly the esterfied form of vitamin A, present in the fish liver oils and their distilled concentrates (*10*) and detected in the circulation of the "dry vitamin A"-supplemented cow (*9*), traverse the placenta more readily than the alcohol form which is suggested (*2*) as the principal form normally present in the circulation of the bovine.

The stability of vitamin A is another factor that perhaps plays a role in storage as well as in transmission. The ester form may be resistant to destructive processes in the placenta and to metabolic activity in the fetus. If this were true, however, the problem of utilization probably would tend to nullify the value of the reserves.

Factors involved in the prenatal nutrition of the bovine fetus are being explored further with the view of overcoming some of the difficulties to which the newborn calf is subject.

Summary. Feeding vitamin A at the rate of a million U.S.P. units daily to individual dairy cows in

the latter stages of gestation augmented significantly the vitamin A concentration in the blood and the livers of their newborn calves, but pasture grazing, providing an abundance of carotene in the prepartum diet of the dams, failed to effect an increase over that observed in calves from dams restricted to a standard winter ration. The explanation for these divergent results is obscure, but it is suggested that the placental membrane may be more permeable to the ester form of vitamin A than to the alcohol form. This high initial vitamin A reserve in the newborn calf should have practical value in the maintenance of its postnatal health.

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The Low Therapeutic Activity of Penicillin K Relative to That of Penicillins F, G, and X, and Its Pharmacological Basis

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Commercial penicillin contains at least four molecular species, identified as F, G, K, and X and differing from each other in the nature of the side group attached to a common nuclear structure (*8*). These are known to vary significantly in their bactericidal activity *in vitro*. Thus, referred to penicillin G as 100, the relative activities per milligram of penicillins F, G, K, and X against *Staphylococcus aureus* are reported to be 90, 100, 140, and 55, respectively (1,550, 1,667, 2,300, and 900 units/mg.) (*7*). In this laboratory, crystalline samples of F, G, K, and X were found to have relative gravimetric activities *in vitro* of 82, 100, 120, and 140 against the C-203 strain of hemolytic streptococcus, and 53, 100, 75, and 50, respectively, against a cultured strain of *Spirochaeta pallida* (Reiter) (*3*).

Subsequently, however, results obtained in the treatment of experimental syphilis indicated differences in the relative activity of the several penicillins *in vivo* far exceeding those hitherto observed *in vitro*. The curative dose (CD_{50}) of commercial penicillins, which probably consisted largely of penicillin G, had been found by Eagle, Magnuson, and Fleischman (*2*) to be 1,650 units/kg. when given every four hours for 20 injections. Almost identical results were obtained by Fleming (*4*), using both commercial penicillin and crystalline G. However, with penicillin K similarly administered preliminary data provided by Chesney (*1*) and confirmed by Mahoney and Arnold (*5*) indicated that even 16,000 units/kg. were not curative.

The obvious explanation for this marked discrepancy between the activities of penicillins G and K seemed to be that penicillin K, despite its definite activity against cultured, nonpathogenic spirochetes, was relatively inactive against pathogenic *S. pallida*. An alternative, if less likely, explanation was that penicillin K might be excreted or destroyed in the body more rapidly than the other penicillins and would therefore be relatively ineffective not only in the treatment of syphilis but in other infections as well. The data here presented indicate that this is in fact the case. Penicillin K disappears from the blood, and presumably the tissue fluids as well, far more rapidly than do the other penicillins; and the relatively small amount excreted in the urine suggests that it is inactivated *in vivo* to a greater degree than penicillins F, G, or X. Finally, corresponding to its pharmacologic behavior, and in complete agreement with the results in experimental syphilis (*5, 9*), it has proved approximately 9 to 15 per cent as active as penicillins F, G, or X in the treatment of experimental pneumococcus or streptococcus infections in white mice.

Preliminary data indicate that the rapid disappearance of penicillin K from rabbit blood and its relatively low recovery in the urine are due to its inactivation by the circulating blood. In rabbits the inactivating agent appears to be a relatively thermolabile, nondialyzable constituent of plasma. It is not present in any of the highly purified protein fractions of human plasma so far tested.

Blood levels and urinary excretion in rabbits. When rabbits were injected intramuscularly with crystalline penicillins F, G, K, and X[1] at equivalent dos-

[1] The following firms have made available samples of crystalline penicillin used in this study: Upjohn (F), Squibb (G), Lederle (X), and Abbott (K). Their cooperation is gratefully acknowledged.

ge (0.6 mg./kg.), essentially similar blood levels were obtained with F, G, and X.

With penicillin K, on the other hand, the blood level fell far more precipitously than with the other three. Thus, one hour after the injection, the blood level in animals injected with K ranged between a minimum of < 0.02 and a maximum of 0.031 μg./cc., averaging approximately 0.02; while in 10 animals receiving the other three penicillins, the blood levels at one hour varied between 0.07 and 0.45 μg./cc., averaging 0.23, or 11 times the average level of K. The length of time for which penicillin remained at a measurable level, e.g. 0.04 μg./cc., averaged 45 minutes with penicillin K, and two hours with the other three penicillins.

The data on the urinary excretion of penicillin in rabbits showed equally pronounced differences between penicillin K, on the one hand, and the other three penicillins on the other. The total cumulative excretion over a period of six hours in six rabbits receiving K varied between 18 and 42 per cent of the total injected and averaged 33 per cent; while in nine rabbits receiving penicillins F, G, and X the corresponding cumulative excretion varied between 39 and 100 per cent and averaged 74 per cent.

Blood levels and urinary excretion in man. Results qualitatively similar to those in rabbits were obtained in six men injected with identical doses of F, G, K, and X (0.6 mg./kg.). With penicillin K, the blood penicillin level one hour after injection varied between < 0.036 and 0.14 μg./cc., averaging 0.08; the corresponding values in the same four patients similarly injected with G were 0.14 to 0.57, with an average of 0.31 μg./cc. In man, the length of time for which the blood contained measurable amounts of penicillin, e.g. 0.04 μg./cc., averaged approximately 70 minutes in the case of penicillin K and was more than two hours with penicillin G.

The differences in the urinary excretion of G and K in man were consistent and marked. In four patients injected with 0.6 mg./kg. of penicillin G, the cumulative percentages excreted in the urine in six hours were 95, 99, 73, and 99, the average being 91 per cent. When the same four patients were injected with an equal amount of K, the corresponding percentages recovered in the urine in six hours were 39, 31, 31, and 22, the average being 31 per cent.

Therapeutic activity of penicillins F, G, K, and X in experimental infections in white mice. One would anticipate from the foregoing data that penicillin K would be relatively inactive *in vivo* in any infection, and regardless of its bactericidal activity *in vitro*. To determine this point, mice heavily infected with pneumococcus Type I and with *Streptococcus pyogenes* were treated with varying doses of penicillins F, G, K, and X. The curative doses (CD_{50}) of penicillins F, G, K, and X in pneumococcus Type I infection were, by the particular method of treatment used, totals of 4, 3.4, 20, and 2.45 mg./kg., respectively. Expressed relative to G as 100, these are gravimetric activities of 85, 100, 17, and 140. Penicillin K was thus one-sixth as active per milligram as penicillin G and one-eighth as active as penicillin K. The sample of penicillin K used in this experiment contained up to 10 per cent of some contaminating penicillin other than K. It follows that the therapeutic activity of pure K would have been even less than that observed.

An even more striking difference between the activity of K and the other three penicillins was observed in the treatment of streptococcal infections in mice. Against that same strain of streptococcus the relative activities of crytsalline F, G, K, and X *in vitro* had been found to be 82, 100, 120, and 140, respectively. Their curative doses (CD_{50}) in infected mice were 2.6, 1.3, 14.9, and 0.5 mg./kg., or relative activities of 50, 100, 9, and 260. Penicillin K was therefore only one-eleventh as active as penicillin G and one-thirtieth as active as penicillin X *in vivo*, despite its high activity against the same organism *in vitro*.

Practical implications. The strain of penicillium most widely used at the present time in the commercial production of penicillin is the Q-176 strain of *Penicillium chrysogenum*. It is stated that up to 50 per cent of the penicillins produced by this strain in the absence of specific precursor substances may be penicillin K. The present data indicate that, with "penicillin" containing such large amounts of K, the actual therapeutic potency *in vivo* may be far less than its activity *in vitro*, measured in staphylococcidal units. With such penicillins, previously effective doses may be therapeutically inadequate, and larger amounts must be administered to achieve the same results.

It is clearly desirable to modify the method of producing penicillin in order to minimize the proportion of K in the final product. If a single molecular species of penicillin cannot be provided, whether F, G, or X, it would be desirable also to use methods of standardization which bear a more direct relationship to therapeutic activity than does the determination of bactericidal activity *in vitro*. The determination in experimental animals of either therapeutic activity or residual blood penicillin, e.g. one hour after the injection of a standard test dose, might suffice for this purpose.

Summary

One hour after the injection into rabbits or man of penicillins F, G, K, and X at 0.6 mg./kg., blood

levels of K were one-fourth to one-eleventh of those observed with the other penicillins, and K persisted at demonstrable levels for relatively short periods.

In both rabbits and man the recovery of K in the urine averaged 30–35 per cent. This compares with an average recovery for F, G, and X of 74 per cent in rabbits and 91 per cent in man.

In the treatment of experimental pneumococcal infections in white mice, an impure preparation of K was one-sixth as active as G and one-eighth as active as X. In the treatment of experimental streptococcal infections in white mice, a pure preparation of K was one-eleventh as active as G, and one-thirtieth as active as X.

The above data suggest that penicillin K is inactivated in the body to a greater extent and more rapidly than either F, G, or X, resulting in a far lower therapeutic activity than would be anticipated from its bactericidal action *in vitro*. It seems clear that the amount of K in commercial penicillin should be minimized; and it would seem desirable to standardize impure mixtures of penicillins for therapeutic use by some method other than their bactericidal activity *in vitro*.

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Direct Culture of Rheumatic Virus[1]

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In March 1945 there was presented before the New York Pathological Society (*4*) a demonstration of specimens and a discussion concerning the production of nonbacterial endocarditis of a verrucous type in experimental animals following the injection of pericardial fluid, whole blood, and blood plasma from patients with rheumatic fever, and the subsequent propagation of the supposed pathogenic agent or agents in embryonated eggs and transfer back to the small mammals to reproduce the disease. It was recognized that virus diseases naturally present in the experimental animals may give rise to difficulty in interpretation of the morphological results, as has been noted by De Vecchi (*3*) and Andrei and Ravenna (*1*); hence the need of supporting evidence.

J. L., girl aged 16, with severe rheumatic endocarditis and pericarditis and temperature of 105.2° was admitted to hospital on 12 January 1946. The plasma of her blood, drawn that evening, was injected into five embryonated eggs on 13 January. Of these eggs, two died on the first day, one on the fourth day and two were killed on the sixth day, so that the result was briefly recorded as $D_1 - D_1 - D_4 - K_6 - K_6$. Another specimen of plasma, taken on the morning of 13 January and injected into five eggs on this day gave the result $D_1 - K_6 - K_6 - K_6 - K_6$; and the third specimen, taken on the afternoon of 13 January and injected without delay into five eggs, gave the result $D_2 - D_2 - K_6 - K_6 - K_6$. On 14 January a fourth specimen, taken in the morning, supplied plasma for five eggs with the result $D_1 - D_3 - K_6 - K_6 - K_6$. A fifth specimen, taken that afternoon, supplied plasma for five more eggs and resulted in $D_2 - D_3 - D_3 - K_6 - K_6$.

None of these eggs showed any recognized pathological changes. The extraembryonic fluids were harvested promptly and found bacteria free by aerobic culture.

On 21 January the pooled fluids from these 25 eggs were used in part for the inoculation of rabbits and guinea pigs and later for inoculation of more embryonated eggs (see below).

Meanwhile, on 15 January some of the citrated plasma saved from the blood drawn on 12 January was used for inoculation of the chorioallantoic membranes of five embryonated eggs, aged 9 days. All five of these eggs survived to be harvested on 18 January ($K_3 - K_3 - K_3 - K_3 - K_3$), and all exhibited remarkable localized thickening of the chorioallantoic membrane and intense reddish-pink discoloration of the embryo proper. Aerobic bacterial cultures remained free from growth. One membrane of this lot was ground in a mortar and suspended in saline solution for inoculation on the chorioallantois of five additional embryonated eggs on 29 January. All these survived to be harvested on 2 February ($K_4 - K_4 - K_4 - K_4 - K_4$), and each exhibited a thickened chorioallantoic membrane with local nodules and general reddening of the live embryo itself.

The pooled fluids of the first 25 eggs mentioned above (21 January) were used in part for injection into five eggs on 26 January, with the result $D_2 - D_2 - D_4 - K_6 - K_6$. No pathological changes were recognized in these eggs. On 26 January, also, this

[1] Aided in part by Grants No. 522 and No. 523 of the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association; and by the Virus Research Fund of the Lambert Pharmacal Company.

me pooled fluid was used to inoculate the chorio-llantoic membrane of five embryonated eggs. The sult was $K_3-K_3-K_3-K_3-K_3$. All these eggs hibited thickened membrane and reddened embryo harvest on 29 January. One of these membranes as ground and suspended in saline solution for in-ulation onto chorioallantois of each of five embryo-ated eggs on 1 February the result being $K_4-K_4-K_4-K_4-K_4$. All five had thick lesions on the chorio-llantois and reddened embryo at harvest.

A further specimen of blood, drawn from the atient on 24 January, supplied plasma for egg in-culations on 26 January. This was injected into ve eggs, with the result $D_2-D_3-D_4-K_6-K_6$. One f these, dying on the fourth day, exhibited a much hickened chorioallantois. The others were free from ecognized gross alterations. Also on 24 January this ame plasma was used to inoculate the chorioallantois n each of five eggs, with the result $K_3-K_3-K_3-K_3-K_3$. Each of these eggs at harvest exhibited ocally thickened membrane and diffuse redness of the mbryo.

The pooled extraembryonic fluid from the first 25 eggs was used in part for intravenous injection into rabbits and intraperitoneal injection into guinea pigs. This experiment is to be reported elsewhere.

The brief title of this note should not be misinterpreted. Rheumatism is a clinical term which has been applied to diseases of diverse causation. Patient J. L. is suffering from a severe first attack of the rheumatic fever of adolescence with evidence of endocardial and pericardial inflammation, a disease entity recognized more or less definitely since the classical description of Bouillaud (*2*). The observations reported here indicate that the blood of this patient has harbored an agent which has been propagated in embryonated eggs with the production of rather characteristic changes in the eggs.

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News and Notes

Editorial Announcement

Next week *Science* will consist of only 32 pages. This reduction in size is forced on us simply because we do not have the paper for the larger journal our readers have come to expect.

Paper supplies, which were scarce enough during the war period, have become even more scanty since controls on consumption were removed.

Strikes in the various industries and services have further added to the acuteness of the scarcity, which is prevalent in all kinds of paper, kraft, newsprint, book, and coated stocks. If it were possible to bring you *Science* printed on wrapping paper, we would do it!

We hope that the emergency will last only a few weeks, but actually at this time, there is no sure way of predicting how long it will last.

Some monthly scientific publications will not be able to print their June issues at the regular time and whether these numbers will appear in July or in August, no one is able to say at the moment.

Ernest W. Goodpasture, professor of pathology and dean of the School of Medicine, Vanderbilt University, Nashville, Tennessee, has been selected as the 1946 recipient of the Passano Foundation Award, according to the Board of Directors of the Foundation. Presentation of the $5,000 cash award was made at an appropriate ceremony in Osler Hall of the Medical and Chirurgical Faculty of Maryland, in Baltimore, on the night of 15 May, when Dr. Goodpasture will speak on "Research and Medical Practice."

The Foundation, which was established in 1944 by the Williams and Wilkins Company, Medical Publishers, of Baltimore, proposes to aid in any way possible the advancement of medical research, especially research that bears promise of clinical application. For the encouragement of such research the Foundation has established the award as one of its activities.

Dr. Goodpasture receives the award for his original development of the method for propagation of viruses in pure culture by inoculation of chick embryos and for his outstanding contributions to advancement of knowledge of the cell-parasite relationship in bacterial and virus infection.

Albert E. Wood, paleontologist, has been appointed assistant professor of biology at Amherst College, effective 15 April 1946. Dr. Wood had been a geolo-

gist with the U. S. Army Flood Control prior to entering the Army in 1942.

Felix Ehrenhaft, physicist, of New York, has been asked to resume his former position as professor at the University of Vienna. This invitation, sent by the Austrian Minister of Education, was forwarded through the Chief of the Education Branch, U. S. Forces in Austria. The letter emphasized that the rights of Austrian professors, who had been dismissed by the Nazis, will be recognized by the present Austrian Government.

Maj. Merrill Moore, Medical Corps, has returned to the United States for a brief tour of duty after three years in the South Pacific and has been reassigned to foreign service as surgeon to the Nanking Headquarters Command. His address is APO 909, Postmaster, San Francisco, California.

A. V. Hill, London, *L. Lapicque,* Paris, and *L. A. Orbeli,* Moscow, have been made honorary members of the American Physiological Society.

H. Munro Fox, F.R.S., chairman of the British National Committee for Biology, left England on 27 March to make a tour of Europe in order to discuss with colleagues on the Continent cooperation in biological science and particularly the future of the International Union for Biology.

Philip W. West will leave in the middle of May to study with Dr. Fritz Feigl in Rio de Janeiro, Brazil. Dr. West will return this fall to resume his duties as head of the Division of Analytical Chemistry at Louisiana State University. During his stay in Rio de Janeiro he will collaborate on researches in Spot Test Analysis. The work will be conducted in the Laboratories of Mineral Productions of the Brazilian Ministry of Agriculture.

Bart J. Bok, of the Harvard Observatory, gave the address following the annual initiation exercises of the Smith College Chapter of Sigma Xi on 10 April. His subject was: "Between the Stars."

Col. Francis R. Dieuaide, recently chief of the Tropical Disease Treatment Branch of the Surgeon General's Office, has been named scientific director of the Life Insurance Medical Research Fund as of 1 April, with offices at 333 Cedar Street, New Haven 11, Connecticut.

The Life Insurance Medical Research Fund was established in 1945 to make grants to universities and medical schools for research on diseases of the heart and related diseases. The Fund plans to make grants of more than $3,000,000 for this purpose over the next five years. A total of 147 life insurance companies in this country and Canada are supporting the Fund.

Coincident with the announcement of Dr. Dieuaide's appointment, M. Albert Linton, chairman of the Fund, announced that the directors had approved a new series of grants totaling $310,000 in support of research work on diseases of the heart and related diseases at 27 institutions in this country and in Canada. This action brings the total of grants made since the Fund was organized to $436,000. Other applications are still under consideration. As scientific director, Dr. Dieuaide will investigate the applications for funds and make recommendations to the group's advisory council.

Isabelo Concepcion has written from the Philippines to Carey D. Miller, of the University of Hawaii Agricultural Experiment Station, Honolulu, as follows:

> As you probably know, Manila is now a ghost city. There are no laboratories or libraries that have survived the destruction of the city. That is the reason why I am so far behind in nutrition literature, and I shall appreciate it very much if you can send me reprints of your work during the past five years and any other literature that will help me in my studies on nutrition and particularly references on the vitamin content of foods, especially on tropical foods.
>
> At present I am studying the adequacy of the food intake of our wage earners and also the incidence of dental fluorosis in the Islands. I am very much interested in the subject of biomicroscopy and its use in the early diagnosis of deficiency diseases.

Dr. Concepcion is now professor of biochemistry in the College of Medice, University of Santo Tomas. His address is: 589 Zamora, Pasay; Rizal, Philippines, where he would like to receive reprints and books.

Carl Gustaf Rossby, of the University of Chicago, internationally famous meteorologist of Swedish birth, will serve as an expert at the newly founded Swedish Government Meteorological-Hydrographical Institute in Stockholm.

Edwin B. Wilson is returning to the United States from Glasgow. He was in residence at the University there from 1 October 1945 to 30 March 1946 to give the Stevenson Lectures on Citizenship.

Jack A. Gerster has accepted the position of assistant professor of chemical engineering at the University of Delaware. He was previously connected with the Du Pont Company and spent a large part of 1944 and 1945 on the Manhattan Project.

Laurence H. Snyder, of the Ohio State University, addressed the Syracuse University Chapter of Sigma Xi on 19 April on the topic: "Human Heredity and Modern Life."

John A. Fleming, director of the Department of Terrestrial Magnetism of the Carnegie Institution of

ashington, was elected a member of the Norwegian cademy of Sciences and Letters in its Section of athematics and Natural Science on 22 March.

Allyn C. Swinnerton, professor of geology at ntioch College, has been awarded the Legion of erit by the War Department. His principal work hile serving in the Signal Corps was in research d development relating to quartz crystals.

Francis G. Gilchrist, of Riverside College, Riverside, alifornia, has been appointed chairman and head of he Department of Biology at Lewis and Clark Col-ge, Portland, Oregon. He will succeed Florence eebles, who retires this year.

Mont A. Cazier has returned to the American Mu-eum of Natural History, New York City, as chair-an and associate curator of the Department of Insects and Spiders.

Robert N. Feinstein has joined the staff of the May Institute for Medical Research, Cincinnati, after four years in the Army. He will be in charge of the bio-chemical aspects of research at the Institute.

Louis Jordan has been appointed executive secretary of the Division of Engineering and Industrial Research of the National Research Council. Mr. Jordan, trained initially as a chemist and metallurgist, was for many years a member of the staff of the metallurgical division of the National Bureau of Standards, directing research in chemical metallurgy and in heat treatment and elevated temperature service of metals. In January 1942 he went to the National Research Council and was responsible throughout World War II for the administrative organization and operation of the War Metallurgy Committee in all of its activities as an advisory committee to OSRD and WPB in the fields of minerals and metals research and development.

Lise Meitner, pioneer atomic scientist now teaching nuclear physics at Catholic University, Washington, D. C., has been elected to the Academy of Sciences of Oslo, Norway, the University announced recently. Dr. Meitner is on a month's lecture tour of colleges throughout the country. Her first lecture was in Cambridge, Massachusetts, before the American Physical Society on 25 April.

Henry Eyring, professor of physical chemistry at Princeton University since 1933, has been named dean of the Graduate School of the University of Utah. In addition to his academic duties at Princeton, Dr. Eyring has been director of technical research instituted at that University. Dr. Eyring is secretary of the Physical and Inorganic Section of the American Chemical Society, vice-president of the AAAS, and chairman of Section C. In 1933 Dr. Eyring won the $1,000 AAAS award given for the best scientific paper of the year.

The Graduate School was created by the University of Utah Board of Regents to replace the Graduate Division, which has been administered by a faculty committee headed by Orin Tugman, head of the Physics Department. Dr. Tugman is retiring from the University faculty.

Charles D. Michener has returned to the American Museum of Natural History, New York City, as associate curator in the Department of Insects and Spiders.

Col. Richard P. Strong was awarded the Legion of Merit on 10 April. As director of Tropical Medicine, Army Medical School, he supervised and participated in the instruction of nearly 2,000 students, including medical officers of five Allied Governments and staff members of American medical colleges.

Tibor Rado will become chairman of the Department of Mathematics at Ohio State University, succeeding John L. Synge, who has resigned, effective 30 September, to head the Applied Mathematics Division of Carnegie Institute of Technology, Pittsburgh.

Robert L. Usinger has resumed his work at the University of California as assistant professor of entomology and assistant entomologist in the Experiment Station, with headquarters on the Berkeley campus. He was released from duty in Malaria Control, U. S. Public Health Service, on 30 April.

Col. George W. Hervey, on duty in the Office of the Chief of Staff, War Department, since October 1944 and previously attached to Headquarters, Army Service Forces, will go on inactive status on 13 June and join the administrative staff of the Surgeon General of the Army in a civilian capacity.

Announcements

The program in Agricultural Science, established at Yale University three years ago but delayed in its development because of the war, will be open to students at the beginning of the next academic year. This program is designed to provide training in the sciences fundamental to agriculture for men planning to enter professional work in this field. The increasing importance of food production in a hungry world and the many technical problems which modern agriculture faces have resulted in a wide demand today for workers with a broad background of scientific training to serve in experiment stations, industrial laboratories, commercial organizations, and other agencies. Such training most men now seek in colleges of agriculture, but other institutions where adequate staff and facili-

ties are available may well offer additional opportunities for work of this sort. Yale is particularly well situated to undertake such a program. The first appointment in what later became the Sheffield Scientific School was that of a professor of agricultural chemistry, and from work thus begun developed the first agricultural experiment station in the country. Yale itself served for some years as a land-grant college.

The curriculum being offered is one of several open to students who elect to major in the biological sciences. It includes work in English and a modern language and offers opportunity in each year for one nonscience elective. In the sciences, basic courses in botany, zoology, chemistry, physics, mathematics, physiology, nutrition, genetics, and soil science are required. In the last two years opportunity is offered for election among a considerable group of courses more closely related to agriculture, including entomology, mycology, plant pathology, economic zoology, parasitology, microbiology, plant and animal improvement, economic botany, plant ecology, agricultural economics, geography, and biometry. These courses will be given by men from various departments of the University, including the Schools of Forestry and Medicine.

No work in the practical or educational aspects of agriculture is proposed, nor is there any attempt to compete in this field with the agricultural colleges. It has been felt that for most students who are going into the agricultural professions, a grounding in the basic sciences is the most important training to obtain during their undergraduate years. Where more technical knowledge of agricultural materials and practices is needed, this can be gained either in graduate work or by direct experience in the laboratory or field. It is hoped that the proposed program will encourage men of high ability and scientific interests to enter a professional career which needs such men but which has not heretofore attracted many students in nonagricultural institutions.—*Edmund W. Sinnott* (Yale University).

A new foundation, The Medical Memorial Fund, has been organized to accept gifts from the public and to distribute its income to the various medical schools and research institutions. It receives its income largely from memorial gifts from the public. As each memorial gift is received, a dignified "Memorial Certificate" is sent to the bereaved family to notify them of the gift. All gifts, whether $5.00 or $5,000, are placed in a general fund to be distributed for research to various medical schools and research laboratories.

The officers of the Fund are: Harlow Shapley, Ph.D., chairman; Henry S. Simms, Ph.D., president; Russell L. Cecil, M.D., vice-president; J. Murray Steele, M.D., vice-president; Marvin R. Thompson, Ph.D., secretary; Guy Emerson, treasurer; J. Murray Steele, M.D., medical director; and John V. Duncan, counsel.

Distribution is determined by a scientific committee aided by various subcommittees and special consultants. A total of about 50 medical scientists cooperate in making decisions concerning the disbursal of grants. Members of the Scientific Committee include: J. Murray Steele, M.D., chairman; A. J. Carlson, Ph.D.; Russell L. Cecil, M.D.; Harry Goldblatt, M.D.; Theodore G. Klumpp, M.D.; Chauncey D. Leake, Ph.D.; William deB. MacNider, M.D.; Marvin R. Thompson, Ph.D.; Henry S. Simms, Ph.D.; D. D. van Slyke, Ph.D.; A. Ashley Weech, M.D.; and George H. Whipple, M.D.

It is estimated that $5,000,000 to $10,000,000 per year could be profitably added to the support of medical research at this time. Medical Memorial Fund is conducting a campaign to raise as much of this as possible. Gifts can be made at any time throughout the year. All scientists and physicians of the country who are interested in an expansion of the medical research program, which will permit greater attention to the cardiovascular-renal diseases, to aging, and to arthritis and rheumatism, should aid the Fund not only by personal gifts but also by advising their friends and patients to make contributions.

Gifts and requests for information should be addressed to: Medical Memorial Fund, 650 West 165th Street, New York 32, New York.

Additional information on prewar and wartime production of synthetic emulsifying agents, wetting agents, detergents, and soap substitutes by the I. G. Farbenindustrie plant at Hoechst, Germany, is now available to the public, according to the Office of the Publication Board, Department of Commerce.

Data on the German developments, gathered by the Combined Intelligence Objectives Subcommittee, are contained in a 38-page report, PB–6684, available from OPB on order (photostat, $3.00; microfilm, $.50). The report is one of several on the same subject on sale by OPB.

The chief organic detergents and emulsifying agents made at the Hoechst plant before the war were "Igepons," derived from oleic acid or substitute materials, and "Igepals," based on ethylene oxide, which was produced from acetylene generated from calcium carbide. "Igepons" were used as leather assistants, washing and softening agents, and detergents. "Igepals" were used as industrial soap substitutes, for washing and soaping vegetable fibers, as dyeing assistants, detergents for wool, emulsion breakers for the petro-

eum industry, textile lubricating oils, and for other purposes.

Of the two types, the "Igepals" were considered superior for use with hard water. The "Igepals" allegedly were superior also to soap in this respect.

Wartime developments included detergents of the alkyl-aryl-sulfonate type and emulsifying agents and detergents from Fischer-Tropsch oils.

"Emulphor STH" and "Emulphor STX," derived from "Mersol," made from by-products of the Fischer-Tropsch synthesis of hydrocarbons from coal, proved valuable for drawing of metals. The Germans claimed that their use eliminated some of the intermediate heat-treating operations and, in many cases, the Parkerizing process employed in metal working.

PB-6684 contains details on types of emulsifiers, wetting agents, and detergents produced, raw materials used, and methods of manufacture.

Mail orders for the report should be accompanied by check or money order, payable to the Treasurer of the United States, and should be addressed to the Office of the Publication Board, Department of Commerce, Washington 25, D. C.

Eli Lilly, president of Eli Lilly and Company, has announced the purchase of government-owned facilities and the Stokely Foods buildings, at West Morris Street and Kentucky Avenue, Indianapolis, Indiana. These were formerly used by the Curtiss-Wright Propeller Division. These buildings, to be known as the Kentucky Avenue Plant of Eli Lilly and Company, cover some 26 acres and include a five-story reinforced concrete manufacturing building, two one-story manufacturing buildings, two office buildings, and two power plants conveniently near facilities of the Belt Railroad. The combined plants will give Eli Lilly and Company an additional 1,000,000 square feet of usable floor space.

The Department of Geology at Syracuse University is joining with Cornell College, Iowa, in conducting summer field courses at Camp Norton in the Wind River Mountains of Wyoming. The field camp has been operated by Neil A. Miner, director, since 1940, but this is the first year that Syracuse University has been a joint sponsor. Dr. Miner continues as director, with the staff consisting of Earl T. Apfel, David M. Delo, and Robert O. Bloomer.

Several field courses in geology are offered, including an elementary course in field methods involving the preparation of a geologic map and a comprehensive report on a selected area. A second course, designated "Field Problems in Geology," is open only to those who have had a field course in geology or its equivalent in practical field work. Field research may also be carried on either for the preparation of a thesis or for purposes of publication. There are two camp sessions, 1–28 July and 1–28 August, respectively. Students may register for either or both terms.

Camp Norton is located about 17 miles northwest of Dubois and 94 miles northwest of Lander, Wyoming. Additional information may be secured by writing Dr. Neil A. Miner, Director, Cornell College, Mount Vernon, Iowa, *or* The Department of Geology, Syracuse University, Syracuse 10, New York.

The Virginia Polytechnic Institute Chapter of the Society of Sigma Xi, at a meeting held 16 April, initiated two projects designed to encourage research at the institution. The first of these was the setting up of a research prize consisting of the V.P.I. Sigma Xi Gold Medal, to be awarded each year for the best piece of research produced by a member of the staff or a graduate student in any of the fields recognized by the Society. The recipient of the prize will be selected by a committee from an outside institution.

The second project initiated was the establishment of a series of research seminars for the Chapter members and invited guests, at which will be presented and discussed the current researches on the campus.

The Ohio Academy of Science met at Ohio State University on 3–4 May for its first meeting since the close of the war. Last year's event was canceled because of travel restrictions. The annual dinner was held on Friday, 3 May, in the Faculty Club, where the group heard the presidential address of J. Ernest Carman, of the Department of Geology at Ohio State.

Research personnel in industry and college teachers are invited to attend a graduate conference at the Agricultural and Mechanical College of Texas, devoted to the behavior of mass spectrometers, electron microscopes, and other electronic devices whose operation depends on the action of electron or ion beams. The lecturers for the conference will be Ladislaw Marton, of the Division of Electron Optics of Stanford University, formerly with the Radio Corporation of America, and John A. Hipple, of the Westinghouse Research Laboratories, in charge of the development of the Westinghouse Mass Spectrometers.

The conference will be conducted by the Electrical Engineering and Physics Departments of A. & M. College for a period of three weeks. Dr. Marton will lecture from Monday, 24 June, through Saturday, 6 July. Dr. Hipple will commence his lectures Monday, 1 July, and will conclude them Saturday, 13 July. During the second week of the conference both Dr. Marton and Dr. Hipple will be lecturing. While it is expected that the entire three weeks of the conference will provide a somewhat unified treatment of the more recent advances in the whole field of electron

and ion ballistics, individuals are welcome to attend the conference for shorter periods of time. Persons primarily interested in electron optical theory, but not especially interested in mass spectrometry, could profitably attend only the first and second weeks of the conference, while those primarily interested in problems connected with the operation of mass spectrometers could enter the conference the second week and remain through the third week. The conference coincides with the last half of the first summer term of the College, enabling anyone wishing to remain to carry a full load in the regular program of the second term commencing 15 July.

A matriculation fee of $8.00 will be charged for the course, and a medical fee of $1.50 for the period will also be collected.

Persons desiring further information on the conference or accommodations are invited to write J. G. Potter, head of the Department of Physics, or M. C. Hughes, head of the Department of Electrical Engineering, Agricultural and Mechanical College of Texas, College Station, Texas. (College Station may be reached on the Southern Pacific or Missouri Pacific Railroads via Dallas or Houston.)

Grants up to $10,000 a year for five years to aid research in agricultural chemistry are being offered to universities and other nonprofit research institutions throughout the country by the Herman Frasch Foundation for Chemical Research, it is announced by the United States Trust Company of New York, trustee of the Foundation.

Recipients of the grants, which will be made for the five-year period beginning 1 January 1947, will be chosen by the trustee with the advice of the American Chemical Society. The amount allotted in each instance will depend on the nature of the project concerned.

Designed to stimulate research which will be of practical benefit to the agricultural development of the United States, the grants are made every five years from a trust fund set up under the will of Elizabeth Blee Frasch in memory of her husband, Herman Frasch, chemist, who invented the process of mining sulphur by steam and who was for many years president of the Union Sulphur Company.

Applications for grants must be submitted before 1 July. Each application should describe the research project the institution desires to undertake, the facilities available for carrying out the project, the qualifications of personnel to be assigned to it, the anticipated time for completion, and an itemized estimate of annual expenditures for salaries, apparatus, supplies, etc.

Proposals are to be sent in duplicate to the United States Trust Company of New York, 45 Wall Stree New York 5, New York.

On 28 May at 10:00 P.M., Eastern Daylight Tim Columbia Broadcasting System will present a fu hour of radio time, "Operation Crossroads." Asid from Vice-Adm. W. H. P. Blandy, who will spea from his flagship en route to Bikini, participants wi include Prof. Einstein and the tail-gunner of the B-2 that devastated Hiroshima; Cdr. Harold E. Stasse and a Minneapolis woman who lost three sons in th war; Harold C. Urey and a college freshman; Lt. Ge George Kenney, U. S. Air Forces, representative t the United Nations' Military Staff Committee, and worker at the Oak Ridge, Tennessee, atom plan These people will speak from the auditorium of th Library of Congress, as will former Secretary of th Interior Harold C. Ickes; United Nations Assembl Delegate Archibald MacLeish; Associate Supreme Court Justice William O. Douglas; Senator Brie McMahon, chairman of the Senate Atomic Energy Committee; Representative H. Jerry Voorhis; Secretary of Commerce Henry A. Wallace; and Mrs. Wendell Willkie.

Present for the event at the Library of Congress will be an audience of distinguished statesmen, educators, scientists, military leaders, writers, diplomats and representatives of the world press.

Eight honorary degrees of Doctor of Science were awarded at the concluding exercises of the Sesquicentennial Celebration of the University of North Carolina, Chapel Hill, on 13 April. Jesse Wakefield Beams, William Walter Cort, Edwin Broun Fred, Hugh Jackson Morgan, George Braxton Pegram, James Stevens Simmons, William Ray Taliaferro, and Robert Sessions Woodworth were the recipients.

The semiannual meeting of the Paleontological Research Institution took place at its headquarters in Ithaca, New York, on Saturday, 6 April.

Announcements were made of: (1) the completion of *Bulletin of American Paleontology*, Vol. 29, No. 116, on "Ordovician Cephalopoda of the Cincinnati region," by R. H. Flower, a publication consisting of 656 pages and 50 full-tone plates; (2) the beginning of presswork on the Jackson Eocene molluscan monograph, with 65 full-tone plates; (3) the availability of G. W. Sinclair's article in *Palaeontographica Americana* on "Canadian Platystrophias"; and (4) the purchase of 20 volumes of Reeve's *Conchologia Iconica* (said to be complete).

The Institution is unfortunately obliged to postpone the duplication of the present plant because of labor conditions and the impossibility of obtaining sufficient building materials.

Recent Deaths

Howard de Forest, emeritus professor of botany at the University of Southern California, died on 4 April in Los Angeles, California.

Alexander A. Baikov, 76, Russian metallurgist and vice-president of the Academy of Sciences, USSR, in 1943, died on 7 April.

William Waddell Duke, 63, known for his allergy research, died on 10 April in Kansas City, Missouri.

Rafael Requena, 66, Venezuelan archaeologist and anthropologist, died on 20 April in New York City.

Fred M. Meader, 70, bacteriologist who figured in the investigation which led to the isolation of "Typhoid Mary," the classical example of a typhoid carrier, died on 26 April in Detroit, Michigan.

William Orrin Emery, 83, organic chemist and amateur botanist, was found dead on 7 May, in Fairfax County, Virginia. Dr. Emery was the object of an extensive search when he did not return from a field trip.

Glacial Map of North America

The publication of the Geological Society of America of the *Glacial Map of North America* (*Science,* 1941, **93**, 303–305) is the fruit of three years of compilation and cooperative effort by a committee of geologists and a two-year publication process under wartime difficulties and restrictions.

The map is published in two sheets, together measuring 79 by 52 inches, and is drawn on a scale of 72 miles to the inch. It is the first map to represent the Pleistocene glacial features of the whole of North America on any but a very small scale. Published in 23 different color conventions, it represents North America from the Aleutians and Bering Strait to Iceland, and from the North Pole to Cape Hatteras and Los Angeles. Major topographic features are shown by form lines on the land and on the sea floor. In this way the relation of the glaciated areas to highlands and to continental shelves is brought out.

Areas glaciated during each of the four Pleistocene glacial ages, and during the sub-ages of the last glacial age, are differentiated in color wherever a basis for differentiation exists. End moraines are shown individually. The extent of glacial lakes, regions overspread by interglacial and postglacial seas, and existing glaciers are shown by areal conventions. Striations, drumlins, eskers, boulder trains, outlets of glacial lakes, and locations of exposures of fossil-bearing interglacial deposits are among the features shown by appropriate symbols.

Additional detailed information is furnished by more than 150 footnotes printed on the face of the map. A number of inset maps are included, among them a map showing the distribution of loess in central United States.

The work as a whole has been designed to provide a continental view of the extent of glaciation and the distribution of glacial features, instead of focusing attention principally on the southern sector of the North American glaciated region, as has been done in the past.

The map constitutes Part 1 of the Geological Society's *Special Papers Series,* No. 60; Part 2, issued with the map, is a 40-page pamphlet containing explanatory notes and a selected bibliography of North American glacial geology. The map and pamphlet are issued free to Fellows of the Geological Society and are sold to others at a price of $2.00 by the Society (419 West 117th Street, New York 27, New York).

Compilation and editing of the map are the work of a committee of American and Canadian geologists, set up late in 1939 by the National Research Council, as follows: R. F. Flint (chairman), W. C. Alden, E. T. Apfel, H. S. Bostock, S. R. Capps, J. W. Goldthwait, L. M. Gould, G. F. Kay (deceased), M. M. Leighton, Frank Leverett (deceased), Paul MacClintock, D. A. Nichols, G. W. H. Norman, F. T. Thwaites, G. W. White, and G. A. Young.

Governmental agencies that cooperated in the assembling of data include the U. S. Geological Survey, the Bureau of Geology and Topography (Canada), and various State and Provincial geological surveys. The base and first draft of the final map were prepared in Ottawa under the supervision of the Bureau of Geology and Topography (Canada).

Funds for compilation and drafting were provided by the National Research Council, the American Geographical Society, and the Geological Society of America.

The map, the implied correlations, and the accompanying bibliography represent the latest available information and the best judgment of the compilers. They are expected to provide a firm basis for further field studies, which should make it possible in time to construct an improved and more nearly complete glacial map of North America.—*Richard Foster Flint* (The Geological Society of America).

In the Laboratory

The Lifwynn Eye-movement Camera

HANS SYZ

The Lifwynn Foundation, Westport, Connecticut

In connection with the investigation of behavior disorders carried on by the Lifwynn Laboratory, accurate photographic recordings of eye movements were a specific requisite. After surveying the field and experimenting with eye-movement cameras constructed by other laboratories, it was found desirable to develop an apparatus which would meet our special needs, namely, the simultaneous recording of the horizontal and vertical components, the velocity and exact course

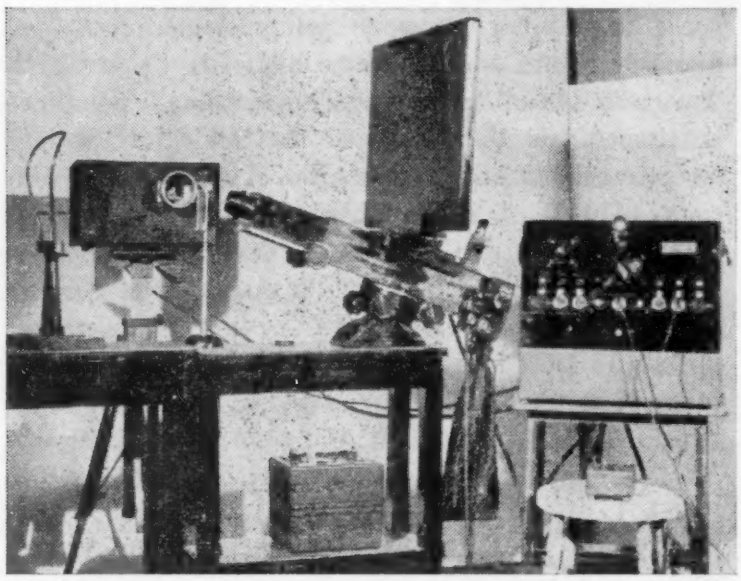

FIG. 1

of motion, and the position and duration of the fixations. It was important not only that these features be recorded simultaneously but also that they be recordable on a single frame and that a quick and easy analysis of each experiment be possible without calculation or other complicated procedures.

The Lifwynn Eye-movement Camera, as shown in Fig. 1, was devised and built by Dr. Henry Roger in his laboratory at Sandy Hook, Connecticut. Mr. Charles Robinson assisted in the development and construction of the electrical features, to be reported in detail in a future communication. The writer participated regularly in the discussion of the distinctive features required to be incorporated in the camera and in progressive experimentation with it.

The apparatus consists of three major parts: a camera with film magazine and frame-changing device, a light source, and an electrical control unit. All parts of the apparatus are interconnected by electrical cables. These are operated and controlled from a central electrical control panel.

The camera incorporates the principle of a still camera and uses 35-mm. motion-picture film. The frame size is 18×24 mm.—that is, the same as is used in regular silent motion-picture cameras. The frame change is activated by a pulldown, operated by a solenoid which is an integral part of the mechanism itself. The frame change is timed to take effect automatically once every second, but by manual control a longer exposure may be obtained.

The frequency of exposures varies from 5 to 30 per second. These frequencies were chosen arbitrarily following a number of experiments which showed that these rates were most likely to permit an adequate analysis of the photographic impressions. However, the number of exposures may be increased to 60 per second and even more if this should seem desirable.

The accuracy of the time intervals between the exposures is quite reliable. It is achieved by an electrically controlled stroboscopic device which lights up a flash lamp at intervals as set by a dial on the control panel.

In order to register the sequence of the eye movements and the duration of the fixations, a rotating dial is employed through which the flashes are projected on the cornea and from there reflected into the camera. The dial, moving clockwise, shows the changing positions of its bar, which can be analyzed readily on the photogram.

In order to secure sharp photographic impressions of this dial on highly sensitized photographic emulsions a very short exposure is required. The powerful light source needed for this purpose was secured by employing a flash tube controlled by a thyratron tube. Disturbing effects of the light flashes are obviated by means of an ultraviolet filter placed in front of the light source.

With regard to its duration, the experiment can be accurately timed within seconds or minutes by a synchronous timer which not only controls the experimental period but also actuates the shutter in the camera, the frame-changing device, and the dial that rotates in front of the light source. It was found advisable that a single turn of the dial, adjusted to one revolution per second, be registered on a single frame to avoid crowding the photogram and making analysis difficult. If, however, one desires to obtain an over-all picture of a subject's eye movements, it is possible to register a longer period on a single frame.

A projection device permits one to superimpose

several frames and also to superimpose the track of the eye movements upon the picture which the subject may be asked to observe during the experiment.

The registration and analysis of eye movements were undertaken as part of the study of the physiological modifications occurring in two forms of attention or adaptation investigated by Burrow and his co-workers. The investigation was undertaken especially with regard to disturbances in attention, as we found that a primary deflection in the process of attention was an invariable accompaniment of disorders of behavior, both individual and social. We had previously found specific alterations of the respiratory function (*1*) and of the electroencephalic potentials (*2, 3*) to be concomitant with these modifications in attention and behavior. These instrumentally measurable and verifiable aspects confirm the distinction made between the two types of attention: (a) *ditention,* as seen in "normal" as well as in neurotic behavior, and (b) *cotention,* which represents the organism's primary phylobiology or its healthy basis of orientation.

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Inactivation of Penicillin by Zinc Salts

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The Oxford investigators and others have reported that penicillin is inactivated by contact with various heavy metals.

In connection with experiments to determine quantitatively the influence of certain pure metals and their salts, we found that the time needed to inactivate the penicillin is quite different for the various metals and salts. The inactivating process depends on different factors and generally takes several days to complete. Zinc salts (*i.e.* sulfate, acetate, chloride, oxide), however, showed an exceptional behavior in our experiments and inactivated penicillin in a short time. That this particular action of the zinc salts, even in such a low concentration as that used under the conditions of our experiments (1/300–1/60 M) has no perceptible bacteriostatic effects calls for special attention. The inactivation with a well-defined, inorganic, easily sterilizable, and stable substance, such as zinc salts, seems to us to be preferable in some cases to procedures with enzymes or other organic compounds; at least, this method may be of interest as a complement or control of another base. The zinc inactivation method is quite useful to us in determining the effects on penicillin of metals and their salts, particularly because in the presence of these substances the use of enzymes sometimes offers serious difficulties. This preliminary report of the "Zn-inactivation method" may be valuable in cases where usual inactivators have thus far been employed.

Experimental Technique

Penicillin: We employed commercial penicillin-sodium of several manufacturers.

Test organism: The H strain of the Oxford investigators or another coagulase positive strain of *Staphylococcus aureus* sensitive to penicillin was used.

Inoculum: Culture media were inoculated with 3 drops (3/50 ml.) of a 12- to 18-hour broth culture.

Culture media: For the serial broth dilution method we used infusion broth (meat infusion and peptone), adjusted to a reaction of about pH 6.5±, distributed as a routine in small test tubes, 2 cc. for each tube. For the Oxford cup method we have employed ordinary nutrient agar (the same infusion broth solidified with 2½ per cent agar).

Zinc sulfate: Sterile solutions in water of $ZnSO_4 \cdot 7H_2O$, 5, 10, 25, and 50 per cent, were employed.

Procedures: The inactivation of penicillin by zinc sulfate can be studied by various simple and satisfactory routine procedures.

In the *Oxford cup method,* to each cubic centimeter of nutrient agar, melted and seeded with *Staph. aureus,* 1/50 ml. of one of the zinc sulfate solutions is added according to the desired concentration. We use for this purpose a capillary pipette, standardized to 1 drop = 1.50/ml. The agar is poured into plates, and the glass cups are placed on the agar and filled with the penicillin solution to be studied. Incubation is at 37°. The inactivation of penicillin is recognized by bacterial growth throughout the whole plate.

An *inverted* cup assay is as follows: To nutrient agar melted and seeded with *Staph. aureus,* as already described, the desired amount of penicillin solution is added. The mixture is poured into plates; glass cups are placed in the agar and filled with the corresponding zinc sulfate solution. Penicillin inactivation is judged by observing a zone of *Staph. aureus* growing around each cup. On the rest of the plate there is no bacterial growth.

The broth dilution method consists of adding 1/50 ml./cc. of one of the zinc sulfate solutions to a single tube with penicillin solution in normal saline or pure water, alone or with body fluids. Incubation is at 37°. After adequate time (12–24 hours or more), serial

dilutions are made out of this tube, and *Staph. aureus* added to each of these. Incubation is at 37°.

A control tube of penicillin solution without zinc sulfate, stored at 37°, during the same time, is used for comparative measuring of the penicillin potency in serial dilution.

Another assay is as follows: Each tube of a range of graduated penicillin dilution is inoculated with *Staph. aureus,* and zinc sulfate solution is added to the tubes immediately (or after a longer or a shorter time). After some hours (4 or more) the tubes are examined for evidence of growth (reading turbidity).

Discussion

In the inactivation of penicillin by zinc salts are involved factors about which we will report in detail later. Thus far our results seem to indicate that penicillin inactivation by zinc sulfate is closely similar in its course to the penicillinase inactivation process. In both cases, curves which derive from the rate of inactivation significantly differ from the straight line.

In the zinc inactivation method, pH and zinc concentration are of primordial importance. The inactivation rate increases with the concentration of the zinc sulfate employed. When strong zinc sulfate solutions are used, their possible antibacterial effect must be considered. Concentrations of 1–5 mg./cc. liquid medium, as used by us, have no bacteriostatic action in our experiments. Lower concentrations have slow or no penicillin inactivation effect at all. Here it will be of interest to mention that very low quantities of zinc sulfate (1–3 mg./liter) had even been recommended for the stimulation of the penicillin production.

A pH between 6 and 6.8 is preferable for the inactivation process and also appropriate for the staphylococcus growth. The broth used by us allowed concentrations of 1–5 mg. of zinc sulfate per cubic centimeter without need for pH correction. It should be noted that in using the zinc concentrations recommended by us, especially the higher ones, zinc hydroxide may be precipitated out. This does not affect the inactivation process; neither does the zinc hydroxide seem to precipitate or adsorb any appreciable quantity of penicillin. On account of this we use in dilution tests the clear supernatant fluid, even though the same results may be obtained using the fluid with the suspended sediment. Under the conditions of our experiments, 1–5 mg. zinc sulfate inactivate in a few hours (12–24 hours) concentrations of the order of 100 units of penicillin. We have obtained the same results whether serum (human), blood (rabbit) or agar were in the medium. This fact, we believe, makes the zinc inactivation method suitable for culturing blood and other body fluids containing penicillin, for the sterility test of penicillin powder, and, perhaps also, a valuable aid in penicillin assay in mixtures of penicillin with other germicides.

Up to the present, as a result of these studies, we cannot say anything substantial concerning the underlying mechanism of the penicillin inactivation. A purely chemical reaction is highly improbable, considering the amounts of zinc salt in relation to penicillin used.

A Note on Staining Plasmodia

A. W. Ratcliffe

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Review of the historical background of malaria has suggested that our conception of plasmodial staining reactions may be incomplete (*3*). The following observations have heightened this impression:

(1) Blood infected with *P. vivax*[1] (produced clinical and typically smear-positive malaria upon therapeutic inoculation), smeared and stained with Wright's stain, was examined by various technicians and by consultant malariologist without recognition of the plasmodium.

(2) Similar blood showed numerous intraerythrocytic organisms, some of which were actively motile, but freshly made and stained smears were searched by a college class in parasitology without demonstration of a single typical parasite.

(3) Smears of blood containing numerous parasites, *P. vivax* (which stained readily when first smeared in Texas), could not, after transportation to Indiana, be stained to show organisms of diagnostic acceptability.

It appeared in this light that solution of the problem of staining these organisms was essential and prerequisite to progress in morphology and also might be helpful in the ancient and recurring problem of smear-negative patients progressing to necropsy demonstration of plasmodia.

Representative of the current concept is the following: "The dilution of the stain and time required for fixing and staining may be varied considerably without changing the quality of the result very much. The pH of the buffer, age of smear, and brand of stain used are important factors which determine the quality of the result" (*2*). Recommendations as to pH range from 7.2 to 6.4. It is indicated that older smears require a lower pH and may require somewhat longer staining time, and that alkaline buffer produces a dark smear while acid buffer produces a red smear.

[1] Indiana Central State Hospital strain, received from Indianapolis as fluid blood.

In recent years the only specific suggestion for staining old blood films seems to be the method of Daniels (1907) which, as outlined by Craig (*1*), calls for a preliminary acid-alcohol bath followed by washing and staining in the usual manner. Repeated trial of these methods did not give the desired result. While the gross appearance of the stained smear is more red with an acid buffer in the range mentioned and darker blue with an alkaline buffer, the red was chiefly that of eosin and the blue largely the result of precipitated stain. Our problem was particularly one of failure to obtain (red) staining of the chromatin. Microscopically, despite the red cast with acid buffers, it was the blue which seemed to stain the nuclei of the leucocytes, rather than the azure components of the stain.

This recalled that hematoxylin, also a nuclear stain, is retarded by acid and precipitated by alkali. Moreover, its staining action is hastened by preliminary rinse of tissue sections in the alkaline bluing bath. Trial of Wright's stain showed clear blue in acid solution but purple with a slight precipitate in alkaline solution. Methyl green was blue in acid but purple in alkaline medium. Azure II showed little change. Azure I and Azure B showed darker blue in the acid solution.

On this basis it seemed that azure-staining of the chromatin might be improved and undue precipitation avoided by using alkali as a preliminary bath rather than as a medium for the stain.

Actual use has verified this principle in several recent clinical cases where typical plasmodia could not be found by routine strain but were present, numerous and well stained after the procedure described.

Sodium carbonate and ammonium hydroxide have both been satisfactory. The concentration is best adjusted by pH determination. Fresh smears will not tolerate strong alkali, and brief exposure to pH 8–9 after fixation may suffice. Older smears are not damaged by considerably stronger alkali and seem to require it for comparable effect. Because of this variation it is not yet possible to be specific as to concentration or time. At present the strength is adjusted to give partial, but not complete, hemolysis. The slide is washed and then stained. For some, the usual time suffices, while for other bloods, prolonged staining is a necessary and helpful factor. This alone gives better results than the routine method, but the use of both the alkali and prolonged staining is distinctly preferable. The nuclei of leucocytes should be distinctly overstained, dark reddish-purple. The staining time is perhaps best controlled by this.

By using several hours in the alkaline bath and 24 hours in Giemsa stain, or a comparable solution of Wright's stain, the parasites brought from Texas in March 1944 have finally been stained to present the desired classical picture.

This seems too useful a tool to withhold, although it needs further development. The possibility of materially hastening the result by adding some penetrant (such as Tergitol-7) is being investigated.

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Letters to the Editor

The Fluorescence of Radium Burns

The fluorescence of scar tissue has been scantly mentioned in past writings in this field. However, it is now widely assumed that cicatrices due to mechanical, electrical, and chemical trauma show little by way of a distinctive response to filtered, long-wave-length, ultraviolet light. Usually tissue damaged by these agents appears lavender or purple to the unaided eye. This excludes the possibility that such scar tissue may contain traces of porphyrins or related substances which would produce a bright red fluorescence, a subject yet open to investigation.

Moreover, it has been assumed that cicatrices due to the effects of X-ray and radium radiations are characterized by a brilliant pearly-white fluorescence under ultraviolet light.

The writer has personally observed numerous instances in which X-ray damage to tissue on various parts of the body fluoresced the pearly-white color. However, it has recently been possible for him to compare the fluorescences of X-ray cicatrices with those caused by radium. In two cases, both adult male and female, tissue damaged in radium therapy not less than 10 years previously exhibited a brilliant light-blue fluorescence under filtered, long-wave-length, *i.e.* 3,650 A., ultraviolet light. In the case of the female, radium irradiation had been employed 15 years previously to remove a small growth on the cheek. The cicatrix was circular, showing a bright-blue fluorescent periphery and a nonresponsive center. The female subject was 25 years of age. In a 55-year-old male, radium had been used 12 years prior for treatment of a growth covering the lower, external

part of the nose. The damaged area also fluoresced the same blue, though the intensity was less pronounced.

From these observations it appears necessary to revise the existing concept of the fluorescence of scar tissue as it pertains to the etiologic factor.

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Fluorescence Laboratories, Portland 5, Oregon

Interesting Observations in Dissections of the Frog

Medical men occasionally amaze the readers of newspapers and journals with reports of interesting anomalies of human anatomy. Students of general zoology are no less amazed to find that Mother Nature sometimes plays havoc with the internal anatomy of some of her lesser creatures.

In 18 years of directing laboratory dissections of the frog, numerous anatomical anomalies have been called to my attention by puzzled students. One of the most interesting cases was the Anuran specimen upon whom the students bestowed the curious name, "Glass-sides." Apparently, in the course of embryological development, the tissues normally laid down to form the laminated muscles, the obliquus externus and internus, had failed to develop. As a result, the internal organs were clearly visible through a thin sheet of mesentery-like tissue, occupying the normal position of the muscle, extending from the dorsal fascia to the linea alba. The animal had developed to normal size at maturity, and although the intestines were held in by little more than the skin, no ruptures had occurred.

Anomalies of the genital system are not common, but in one male specimen the right testis was lacking. In this same animal the position of the stomach was reversed from left to right.

In the above-mentioned anomalies and in numerous other cases of missing or misplaced organs the animals had developed to normal size and were not apparently affected by these defects.

JAMES A. MULLEN
Biological Laboratory, Fordham University

The Plainview, Texas, Fossil Bison Quarry

A fossil bison quarry at Plainview, in Hale County, Texas, discovered in 1944, was excavated during 1945 by the Bureau of Economic Geology of the University of Texas and the Texas Memorial Museum. The quarry yielded skeletons, in varying degrees of completeness, of between 50 and 100 bison of an extinct species appreciably larger than the modern buffalo. The bison skeletons were found in the filled valley of a stream at a depth of 12 feet. The unusual accumulation of skeletons may have resulted from a bison stampede. With the bison were found 19 projectile points and 8 other artifacts, chiefly or entirely scrapers. The projectile points, while resembling the known Folsom and Yuma points used by prehistoric hunters, are distinctive and have been named Plainview points (*Geol. Soc. Amer. Bull.*, 56, 1196).

Bison material to the amount of about three tons, as packed for shipment, was removed from the quarry. Included were eight blocks of bones showing the full thickness of the bone bed. Two of these blocks, containing artifacts in place among the bones, will be placed on exhibit in the Texas Memorial Museum at Austin. With this new material the Memorial Museum will have exhibits of "Early Man" and associated fossils from four Texas localities: Malakoff, Henderson County; Cowan Ranch, Roberts County; Berclair terrace of Blanco Creek, Bee County; and Plainview, Hale County.

The only vertebrate fossil found immediately with the bison bones at Plainview is a large wolf, although the same deposits, near by, here yielded the Columbian elephant, *Parelephas columbi*, and a fossil horse, *Equus sp.* as well as an additional artifact, a scraper. Only fragmentary remains have been recovered of the wolf and the species has not been determined. It is apparently smaller than the great wolf, *Aenocyon ayersi*, found with human materials at the Bee County locality and at Vero Beach, Florida (*Science*, 1916, 44, 615). The Columbian elephant has been found near, or in association with, human relics at all of the localities here mentioned.

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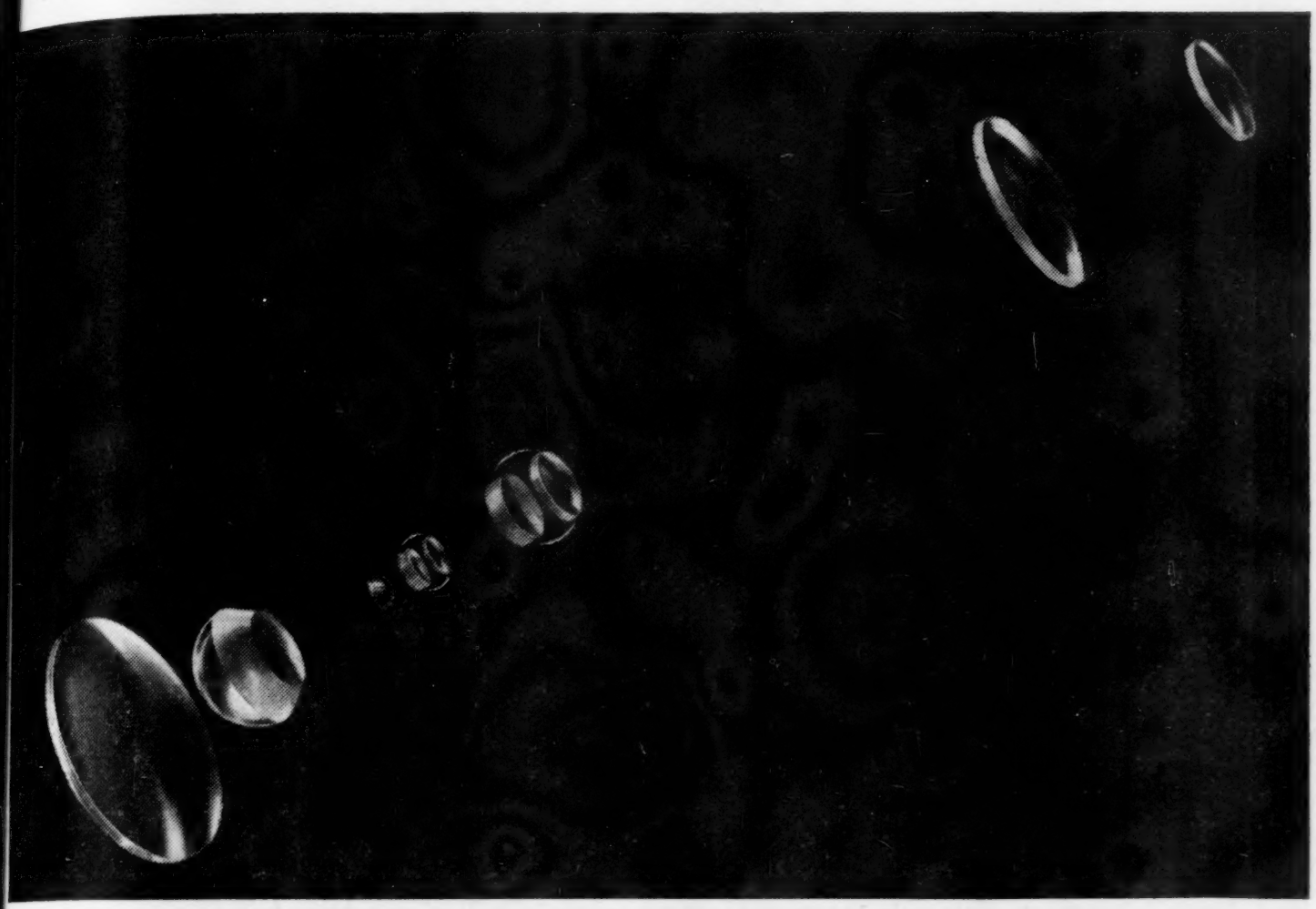
On "The Rumbling of Thunder"

In a recent article by Samuel R. Cook (*Science*, 1946, **103**, 26–27) a "new cause" for the rumbling of thunder is described. He states that he believes this "new cause" to be "more potent" than any of the four causes usually named. This letter is not to dispute either the existence or potence of the new cause, but to raise some further possible questions concerning it.

In the first place, if we assume Mr. Cook's cause to to be the only cause of rumbling, we would logically expect an even distribution of rumblings with the loud clap and diminuendo and those with a crescendo followed by a loud clap. We should also expect many in-between rumblings. This writer has not observed these phenomena in this locality.

In the second place, assuming the arrangement of electrons in the discharge as described (N, 2N, 4N, 8N, . . .), we wonder about the distances between the points where these charges occur. Let us fix the number of electrons at the second cloud as 2^kN. Then, from the loudness of the clap and the rapid diminuendo, must we assume that the distance between the points of 2^kN electrons and $2^{(k-1)}$N electrons is much shorter than that between the points for N and 2N electrons? Or are we to assume that the distances are random and that this can account for the fluctuations in the loudness of the rumbling?

Finally, the time of continuation of the rumbling needs some consideration. Let us assume two cumulus clouds 6,000 feet up and two miles apart, with the second cloud immediately over the observer—an extreme condition. Then the clap should be heard 5 to 6 seconds after the flash is seen, and the rumbling, if all is audible, for 11 to 12 seconds. But considering the



These are the optical elements of a monocular microscope—condenser, objective and eyepiece

weakness of the original discharges, the distance covered, absorption in the atmosphere, how much of it will be audible?

Just what relationship exists among these five factors in the rumbling of thunder, if this relationship can be determined definitely, should prove most interesting.

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A New and Effective Hemostatic Agent

Local agents for the control of bleeding have fallen within three groups: (1) physical, such as pressure; (2) protein precipitating, such as Monsel's solution or tannic acid; (3) coagulation accelerators, such as fibrinogen or thromboplastin. Alginic acid derived from marine kelp may be added to the latter group.

When seaweed is broken or damaged in the water, the injury is healed by the plant juices coming into contact with the calcium ion of the sea water. While the alginic acid may be a transitional product in the synthesis of the carbohydrate of the plant, it also acts as a protective colloid and guards the plant against injury. This clotting and healing action may be likened to that of glycoproteins in the animal and the gums of land plants such as cherry, peach, and acacia.

Alginic acid prepared as a powder and applied to bleeding points combines with the calcium and immediately forms a coagulum that seals the wound. The styptic action is prompt, and new tissue is formed. It has been suggested that the nonirritating character of the coagulum is due to a detoxifying property characteristic of acids derived from kindred carbohydrates such as glucuronic acid.

Alginic acid has been used on a series of 100 cases of extraction and minor oral surgery of the mouth. In no case has there been untoward reaction; healing has been unusually prompt and the control of bleeding an added comfort to both patient and operator.

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Actualités Medico-chirurgicales

At this time, when scientists in formerly occupied countries find great difficulty in bringing themselves up to date on advances that have occurred during the war, it seems appropriate to mention one program designed to this end which has already been under way for some months. Due to the initiative of Prof. E. J. Bigwood, of the University of Brussels, who came to this country during the war, a series of pamphlets, *Actualités medico-chirurgicales,* have been printed here in the French language and are being circulated in Belgium under the joint sponsorship of the Belgian-American Foundation in New York and the Fondation Franqui of Brussels. The authors have been principally American, and the translation has been made by Belgian scientists in this country. Both authors and translators have donated their services. Pamphlets on blood transfusion, penicillin, sulphonamides, protein metabolism, parenteral feeding, viruses, chem therapy, and pyrogens have already been printed, whi others on burns, tuberculosis, DDT, neurology, cance virus diseases, and infant psychology are scheduled appear in the near future. The pamphlets are designe to provide brief surveys to orient the readers to the ne developments in a general way, or as a starting point fo those who may need to go further into the literatur The pamphlets have been very well received in Belgium and a limited number have been sent to other countrie

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Note on the "Purple" Test for Alloxan

In studying further the "purple" test for alloxa previously described (*Science,* 1945, 101, 536; *Arch Biochem.,* 1945, 8, 1), we have come to recognize that i iron is present in the solution tested, it may constitut an interfering factor since it gives rise to an evanescen violet color.

The test, as applied to alloxan, consists in reductio by means of cysteine hydrochloride or ascorbic aci followed by the addition of barium hydroxide to slig alkalinity; a purple color or purple precipitate is the formed. E. Baumann (*Z. physiol. Chem.,* 1883–84, 8 299) discovered that an aqueous solution of cystein gives a blue color with ferric chloride, and V. Arnol (*Z. physiol. Chem.,* 1910–11, 70, 314) observed that, o making alkaline, this blue changes to a violet whic quickly fades but reappears on shaking. Ascorbic aci also gives a violet color under these conditions (R. W Herbert, *et al. J. chem. Soc.,* 1933, 1270).

Hence, the test is likely to lead to erroneous conclu sions if applied to extracts containing iron.

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The Record and the Metric System

Under "Scanning Science" (*Science,* 1946, 103, 446) I notice that a few dates have been omitted. At least two of them are of major importance. In 1866 Congress passed a bill making the metric system lawful in the United States. In the same year Congress directed the Treasury to furnish to each state a set of standard weights and measures of the metric system. In 1893 the Treasury issued an order recognizing the meter and kilogram as fundamental standards and that the customary units will be derived from them.

As to coinage, in 1866 Congress fixed the weights of the 5-cent piece at 5 grams. In 1873 Congress fixed the weights of other coins as follows: half dollar, 12.5 grams; quarter dollar, 6.25 grams; and the dime, 2.5 grams.

In the "Scanning Science" mentioned, the omission of the above facts may give unwarranted comfort to opponents of the metric system.

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The Use of Aircraft for Oceanographic Surveys

In the course of some test work with the Catalina Patrol Bomber (Navy PBY) it occurred to the writers that oceanographic surveys of a physical, chemical, and biological nature could be made to advantage, using such aircraft, rather than boats, as an observation vehicle. The advantages to such a procedure are: greater speed, operating economy, simultaneity of observation, and possibility of obtaining data from remote areas.

The question of making observations on sea water for temperature, conductivity, etc. by means of a drag from the airplane at speeds of 90 mph or more can be answered by the suitable design of such drags. The aircraft can safely operate at very low altitudes above the sea in fair weather; hence, relatively short lines with small tear-drop-shaped metal bobs can be dragged in the water without difficulty by these planes at 100 mph. If thermocouples, conductivity cells, etc. were built into these bobs, the whole assembly could be connected to a small winch in the plane and dragged at desired depths. Water samples could be obtained with a similar arrangement.

A few technical characteristics of the aircraft are given below in order to permit assessment of the possibilities of using PBY aircraft for surveys. The maximum range is about 2,500 miles; maximum endurance (time in the air), 24 hours; operating speed range, 85–150 mph; useful load (including fuel), in excess of 10,000 lbs. Such aircraft are now surplus and could, presumably, be obtained for a very nominal figure. Living and messing facilities are limited, but are adequate to care for flights up to 24 hours duration. Adequate space would be available for scientific instruments and a technical group of four or five persons.

In quiet water areas the aircraft can land on the open sea and can be either moored for a while or taxied along at low speeds. It is not suggested that the PBY be used for open sea work in general. It is more suited to the needs of small stations which cannot afford the expense of a large survey ship and its crew, yet which desire to make observations within a radius of 1,000 miles or so. There are other amphibious aircraft which would be entirely suitable for world-wide operations.

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Notice About Sending Reprints to Austria

Prof. Kisser's plea for reprints (*Science,* 1946, **103,** 337) sets me to wonder how one does send reprints to Austrian scientists. When I mailed one to a member of the faculty of the Hochschule für Welthandel in Vienna, it was returned to me from the New York 1 Post Office with a sticker referring to the Postal Bulletin of 15 January 1946, which apparently prohibits the mailing of printed matter.

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[Science has checked with the U. S. Post Office, which bears out Dr. Fromm's statements: only one-ounce, first-class mail is accepted for Austria.]

Book Reviews

The heating of steel. M. H. Mawhinney. New York: Reinhold, 1945. Pp. viii + 265. (Illustrated.) $4.75.

This book treats the heating of steel in an interesting and thorough manner and brings the reader up to date on the technological progress made in this important field during the past 20 years. An outstanding chapter covers the chemical effects of heating steel and includes an excellent review of the present status of atmosphere control. Other chapters relate to fuels and burner equipment, temperature distribution and furnace control, heat transfer and fuel economy, the quenching of steel, alloys and refractories, and steel mill furnaces.

Among those who will find this book of practical value are steel engineers and metallurgists, operating and maintenance personnel, combustion engineers, and furnace designers, as well as research and development engineers interested in steel-heating problems.

The author predicts that the future trend in fuel technology as applied to industrial heating furnaces will probably be toward application of the cheaper fuels to large heating furnaces for temperatures above 2,000° F. For intermediate temperatures (about 1,800° to 2,000° F.) fuel oil and coke-oven gas—the latter used directly, as in the steel mills, or mixed with other gases as supplied by utilities—will probably compete on a straight price basis with the clean gases, such as natural gas, artificial gas, and butane. At still lower temperatures the author states that convection heating is the most logical method for heat transfer.

While the emphasis throughout is on fuel-fired furnaces, attention is given to salt-bath furnaces, electrical resistance heating furnaces, and induction heating. With respect to the last two items it would appear that a more complete treatment would have been well justified.

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Handbook of nonferrous metallurgy. Pt. II: *Recovery of the metals.* (2nd ed.) Donald M. Liddell. (Ed.) New York: McGraw-Hill, 1945. Pp. xi + 721. $7.00.

The second volume of the new edition of the *Handbook of nonferrous metallurgy* deals with the applications of the principles and processes, described in the first volume, to the particular problems arising in the extraction of metals from their ores. This separation of the subject into two parts, one dealing with principles and the other with their application, is an excellent method of presentation. Since publication of the first edition in 1926 this has been one of the best reference works in the field of nonferrous metallurgy. The revised edition, written during the war, has not, in the opinion of this reviewer, done justice to the excellent reputation of the first edition. Undoubtedly the contributors to this volume could not afford to take the necessary time from their essential war activities to make this edition as complete as they wished. Also, they were compelled to omit certain new processes for reasons of military secrecy.

The book contains separate chapters on the principal methods of recovery used for the more important nonferrous metals (copper, lead, zinc, aluminum, magnesium, gold, and silver). The other metals are grouped into several chapters according to their importance and the type of recovery employed. Each chapter is written by a person (or persons) familiar with the particular process involved. This has some advantages, but leads to much nonuniformity in presentation. For example, considerable information is given on the physical and mechanical properties of aluminum and magnesium alloys, while no such information for copper alloys is presented. There is very little information about the production economics of the important metals, although a summary of such information is given for antimony and for tin. The authors of some chapters go into the methods of chemical analysis in great detail, while no methods of analysis are given for some other metals. The bibliographies of some chapters have been brought up to date, while for other chapters the bibliographies are the same as those in the 1926 edition or are omitted entirely. This lack of consideration for the contributors of valuable articles appearing in recent years is unpardonable. In some cases the references are incomplete, the author and date being omitted. In many chapters, undue attention is given to elementary and irrelevant topics, while the treatment of the actual metallurgical operations is inadequate. An example is a long discussion of blast-furnace copper smelting, now almost obsolete, with only a very brief mention of magnesite brick, suspended-arch construction of reverberatory roofs—one of the most important recent advances in copper smelting. The importance of scrap as a source of the metals is underemphasized or completely neglected. Many of the illustrations are so poorly chosen that they defeat their purpose, and there has been no attempt at uniformity in the presentation of flow sheets and diagrams.

The chapter on antimony is well written, but its length is out of proportion to the relative importance of the metal.

For the most part, the book does not indicate the progress, although slight in many cases, which has taken place in nonferrous metallurgy in the last 20 years. In the opinion of this reviewer, the book was assembled too quickly and was very poorly edited. It will be of limited value to students, engineers, or teachers.

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